Smoking More Harmful Than Sedentary Lifestyle

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FROM THE ANNUAL MEETING OF THE INTERNATIONAL SOCIETY ON HYPERTENSION IN BLACKS

CRYSTAL CITY, VA. – The combination of smoking and an active lifestyle was associated with significantly worse lung function than was the combination of nonsmoking and a sedentary lifestyle in blacks, on the basis of data from more than 3,000 participants in the Jackson Heart Study.

Previous studies have shown that the poor lung function associated with a sedentary lifestyle can significantly predict cardiovascular problems, said Brenda Campbell Jenkins, Ph.D., and her colleagues at Jackson (Miss.) State University. Additional research suggests that blacks might be especially vulnerable to lung damage from smoking, they noted.

But no study has examined the combined effects of smoking and sedentary lifestyle and their effects on lung function, Dr. Campbell Jenkins said in an interview.

"We know that among African Americans there is a low prevalence of smoking and a high prevalence of sedentary lifestyle," she said.

In this study, the researchers examined the joint effect of smoking and sedentary lifestyle on heart health in blacks, using data from the Jackson Heart Study, a population-based observational study including black adults aged 21-94 years living in the area of Jackson, Miss.

The researchers measured pulmonary function using forced vital capacity (FVC) and forced expiratory volume per second (FEV_1). The study findings were presented in a poster at the meeting.

The participants were divided into four groups: nonsmoking nonsedentary, nonsmoking sedentary, smoking nonsedentary, and smoking sedentary. Sedentary lifestyle was defined as the lowest quartile of physical activity.

The mean percentages of predicted FEV_1 values in women in the nonsmoking nonsedentary, nonsmoking sedentary, smoking nonsedentary, and smoking sedentary groups were 95%, 94%, 89%, and 85%. The differences between women in the nonsmoking sedentary and in the smoking nonsedentary groups were significant after controlling for multiple variables.

The mean percentages of predicted FVC values in women in the nonsmoking nonsedentary, nonsmoking sedentary, smoking nonsedentary, and smoking sedentary groups was 94%, 92%, 89%, and 88%, respectively.

The differences between women in the nonsmoking sedentary and in the smoking nonsedentary groups were significant after adjustment for multiple variables.

For men, the mean percentages of predicted FEV_1 values in the four groups were 93%, 89%, 88%, 76%, respectively, but these differences were not significant. In addition, the mean percentages of predicted FVC values in each group were 91%, 88%, 91%, and 80%, respectively, and these differences were not significant.

However, after controlling for multiple variables, the mean FEV_1 to FVC ratio was significantly higher among men in the nonsmoking sedentary group, compared with the smoking nonsedentary group (78.8 vs. 77.5).

Based on these findings, smoking and sedentary lifestyle were both negatively associated with lung function, but smoking tended to have more harmful effects, which was consistent with the literature, noted Dr. Sarpong, director, co–principal investigator, and senior biostatistician of the Jackson Heart Study.

However, more research is needed to determine the clinical implications of the findings.

Study participants were enrolled during 2000-2004. The current study included 1,191 men and 2,065 women aged 21-93 years (average, 54 years). Participants with prevalent cardiovascular disease, asthma, and incomplete measures of smoking or lung function were excluded.

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reported in at least 2% of patients in placebo-controlled trials who received ARICEPT and for which the rate of occurrence was greater for patients treated with ARICEPT than with placebo. **Table 4. Adverse Events Reported in Controlled Clinical Trials in Severe Alzheimer's Disease in at Least 2% of Patients Receiving ARICEPT and at a Higher Frequency than Placebo Treated Patients (Body System/Adverse Event: Placebo [n=392], ARICEPT [n=501], respectively): Percent of Patients with any Adverse Event: 73, 81. Body as a Whole:** Accident (12, 13); Infection (9, 11); Headache (3, 4); Pain (2, 3); Back Pain (2, 3); Fever (1, 2); Chest Pain (<1, 2). **Cardiovascular System:** Hypertension (2, 3); Hemorrhage (1, 2); Syncope (1, 2). **Digestive System:** Diarrhea (4, 10); Vomiting (4, 8); Anorexia (4, 8); Nausea (2, 6). **Hemic and Lymphatic System:** Ecchymosis (2, 5). **Metabolic and Nutritional Systems:** Creatine Phosphokinase Increased (1, 3); Dehydration (1, 2); Hyperlipemia (<1, 2). **Nervous System:** Insomnia (4, 5); Hostility (2, 3); Nervousness (2, 3); Hallucinations (1, 3); Somnolence (1, 2); Dizziness (1, 2); Depression (1, 2); Confusion (1, 2); Emotional Lability (1, 2); Personality Disorder (1, 2). **Skin and Appendages:** Eczema (2, 3). **Urogenital System:** Urinary Incontinence (1, 2). **Other Adverse Events Observed During Clinical Trials** ARICEPT has been administered to over 600 patients with severe Alzheimer's disease during clinical trials of at least 6 months duration, including three double-blind placebo-controlled trials, two of which had an open label extension. All adverse events occurring at least twice are included, except for those already listed in Table 4, COSTART terms too general to be informative, or events less likely to be drug related. Events are classified by body system using the COSTART dictionary and listed using the following definitions: *Frequent adverse events* - those occurring in at least 1/100 patients; *Infrequent adverse events* - those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to ARICEPT treatment and in most cases were observed at a similar frequency in placebo treated patients in the controlled studies. **Body as a Whole:** *Frequent:* abdominal pain, asthenia, fungal infection, flu syndrome; *Infrequent:* allergic reaction, cellulitis, malaise, sepsis, face edema, hernia. **Cardiovascular System:** *Frequent:* hypotension, bradycardia, ECG abnormal, heart failure; *Infrequent:* myocardial infarction, angina pectoris, atrial fibrillation, congestive heart failure, peripheral vascular disorder, supraventricular extrasystoles, ventricular extrasystoles, cardiomegaly. **Digestive System:** *Frequent:* constipation, gastroenteritis, fecal incontinence, dyspepsia; *Infrequent:* gamma glutamyl transpeptidase increase, gastritis, dysphagia, periodontitis, stomach ulcer, periodontal abscess, flatulence, liver function tests abnormal, eructation, esophagitis, rectal hemorrhage. **Endocrine System:** *Infrequent:* diabetes mellitus. **Hemic and Lymphatic System:** *Frequent:* anemia; *Infrequent*: leukocytosis. **Metabolic and Nutritional Disorders:** *Frequent:* weight loss, peripheral edema, edema, lactic dehydrogenase increased, alkaline phosphatase increased; *Infrequent:* hypercholesteremia, hypokalemia, hypoglycemia, weight gain, bilirubinemia, BUN increased, B_{12} deficiency anemia, cachexia, creatinine increased, gout, hyponatremia, hypoproteinemia, iron deficiency anemia, SGOT increased, SGPT increased. **Musculoskeletal System:** *Frequent:* arthritis; *Infrequent:* arthrosis, bone fracture, arthralgia, leg cramps, osteoporosis, myalgia. **Nervous System:** *Frequent:* agitation, anxiety, tremor, convulsion, wandering, abnormal gait; *Infrequent:* apathy, vertigo, delusions, abnormal dreams, cerebrovascular accident, increased salivation, ataxia, euphoria, vasodilatation, cerebral hemorrhage, cerebral infarction, cerebral ischemia, dementia, extrapyramidal syndrome, grand mal convulsion, hemiplegia, hypertonia, hypokinesia. **Respiratory System:** *Frequent:* pharyngitis, pneumonia, cough increased, bronchitis; *Infrequent:* dyspnea, rhinitis, asthma. **Skin and Appendages:** *Frequent:* rash, skin ulcer, pruritus; *Infrequent:* psoriasis, skin discoloration, herpes zoster, dry skin, sweating, urticaria, vesiculobullous rash. **Special Senses:** *Infrequent:* conjunctivitis, glaucoma, abnormal vision, ear pain, lacrimation disorder. **Urogenital System:** *Frequent:* urinary tract infection, cystitis, hematuria, glycosuria; *Infrequent:* vaginitis, dysuria, urinary frequency, albuminuria. **ARICEPT 23 mg/day *Moderate to Severe Alzheimer's Disease*** ARICEPT 23 mg/day has been administered to over 1300 individuals globally in clinical trials. Approximately 1050 of these patients have been treated for at least three months and more than 950 patients have been treated for at least six months. The range of patient exposure was from 1 to over 500 days. **Adverse Events Leading to Discontinuation** The rate of discontinuation from a controlled clinical trial of ARICEPT 23 mg/day due to adverse events was higher (18.6%) than for the 10 mg/day treatment group (7.9%). The most common adverse events leading to discontinuation, defined as those occurring in at least 1% of patients and greater than those occurring with 10 mg/day are shown in Table 5. **Table 5. Most Frequent Adverse Events Leading to Discontinuation from a Controlled Clinical Trial by Treatment Group (Dose Group: 23 mg/day ARICEPT, 10 mg/day ARICEPT, respectively): Safety Population:** 963, 471. **Event/%Discontinuing:** Vomiting (3, 0); Diarrhea (2, 0); Nausea (2, 0); Dizziness (1, 0). The majority of discontinuations due to adverse events in the 23 mg group occurred during the first month of treatment. **Most Frequent Adverse Events Seen in Association with the Use of 23 mg/day** The most common adverse events, defined as those occurring at a frequency of at least 5%, include nausea, diarrhea, vomiting, and anorexia. These adverse events were often of mild to moderate intensity. **Adverse Events Reported in Controlled Trials** The events cited reflect experience gained under closely monitored conditions of a controlled clinical trial in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ. Table 6 lists adverse events that were reported in at least 2% of patients who received 23 mg/day of ARICEPT and at a higher frequency than those receiving 10 mg/day of ARICEPT in a controlled clinical trial that compared the two doses. In this study, there were no important differences in the type of adverse events in patients taking ARICEPT with or without memantine. **Table 6. Adverse Events Reported in a Controlled Clinical Trial in Moderate to Severe Alzheimer's Disease in at Least 2% of Patients and Higher in the 23 mg/day Group (Body System/Adverse Event: 23 mg/day ARICEPT, 10 mg/day ARICEPT, respectively): Safety Population: 963, 471. Percent of Patients with any Adverse Event:** 74, 64. **Gastrointestinal disorders:** Nausea (12, 3); Vomiting (9, 3); Diarrhea (8, 5). **General disorders and administration site conditions:** Fatigue (2, 1); Asthenia (2, 1). **Injury, poisoning and procedural complications:** Contusion (2, 0). **Investigations:** Weight decreased (5, 3). **Metabolism and nutrition disorders:** Anorexia (5, 2). **Nervous system:** Dizziness (5, 3); Headache (4, 3); Somnolence (2, 1). **Psychiatric disorders:** Insomnia (3, 2). **Renal and urinary disorders:** Urinary incontinence (3, 1). **Postmarketing Experience:** Voluntary reports of adverse events temporally associated with ARICEPT that have been received since market introduction that are not listed above, and for which there are inadequate data to determine the causal relationship with the drug include the following: abdominal pain, agitation, cholecystitis, confusion, convulsions, hallucinations, heart block (all types), hemolytic anemia, hepatitis, hyponatremia, neuroleptic malignant syndrome, pancreatitis, and rash. **DRUG INTERACTIONS *Effect of ARICEPT on the Metabolism of Other Drugs:*** No *in vivo* clinical trials have investigated the effect of ARICEPT on the clearance of drugs metabolized by CYP 3A4 (e.g. cisapride, terfenadine) or by CYP 2D6 (e.g. imipramine). However, *in vitro* studies show a low rate of binding to these enzymes (mean K_i about 50-130 μM), that, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interference. Whether ARICEPT has any potential for enzyme induction is not known. Formal pharmacokinetic studies evaluated the potential of ARICEPT for interaction with theophylline, cimetidine, warfarin, digoxin and ketoconazole. No effects of ARICEPT on the pharmacokinetics of these drugs were observed. ***Effect of Other Drugs on the Metabolism of ARICEPT:*** Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, inhibit donepezil metabolism *in vitro*. Whether there is a clinical effect of quinidine is not known. In a 7-day crossover study in 18 healthy volunteers, ketoconazole (200 mg q.d.) increased mean donepezil (5 mg q.d.) concentrations ($AUC_{0\text{-}24}$ and C_{max}) by 36%. The clinical relevance of this increase in concentration is unknown. A small effect of CYP2D6 inhibitors was identified in a population pharmacokinetic analysis of plasma donepezil concentrations measured in patients with Alzheimer's disease. Donepezil clearance was reduced by approximately 17% in patients taking 10 or 23 mg in combination with a known CYP2D6 inhibitor. This result is consistent with the conclusion that CYP2D6 is a minor metabolic pathway of donepezil. Inducers of CYP 2D6 and CYP 3A4 (e.g., phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital) could increase the rate of elimination of ARICEPT. Formal pharmacokinetic studies demonstrated that the metabolism of ARICEPT is not significantly affected by concurrent administration of digoxin or cimetidine. ***Use with Anticholinergics:*** Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications. ***Use with Cholinomimetics and Other Cholinesterase Inhibitors:*** A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol. **USE IN SPECIFIC POPULATIONS *Pregnancy:* Pregnancy Category C:** There are no adequate or well-controlled studies in pregnant women. ARICEPT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Oral administration of donepezil to pregnant rats and rabbits during the period of organogenesis did not produce any teratogenic effects at doses up to 16 mg/kg/day (approximately 6 times the maximum recommended human dose [MRHD] of 23 mg/day on a mg/m^2 basis) and 10 mg/kg/day (approximately 7 times the MRHD on a mg/m^2 basis), respectively. Oral administration of donepezil (1, 3, 10 mg/kg/day) to rats during late gestation and throughout lactation to weaning produced an increase in stillbirths and reduced offspring survival through postpartum day 4 at the highest dose. The no-effect dose of 3 mg/kg/day is approximately equal to the MRHD on a mg/m^2 basis. ***Nursing Mothers:*** It is not known whether donepezil is excreted in human breast milk. Caution should be exercised when ARICEPT is administered to a nursing woman. ***Pediatric Use:*** The safety and effectiveness of ARICEPT in children have not been established. ***Geriatric Use:*** Alzheimer's disease is a disorder occurring primarily in individuals over 55 years of age. The mean age of patients enrolled in the clinical studies with ARICEPT was 73 years; 80% of these patients were between 65 and 84 years old, and 49% of patients were at or above the age of 75. The efficacy and safety data presented in the clinical trials section were obtained from these patients. There were no clinically significant differences in most adverse events reported by patient groups ≥ 65 years old and < 65 years old. ***Lower Weight Individuals:*** In the controlled clinical trial, among patients in the ARICEPT 23 mg treatment group, those patients weighing < 55 kg reported more nausea, vomiting, and decreased weight than patients weighing 55 kg or more. There were more withdrawals due to adverse events as well. This finding may be related to higher plasma exposure associated with lower weight. **OVERDOSAGE Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug.** As in any case of overdose, general supportive measures should be utilized. Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. Tertiary anticholinergics such as atropine may be used as an antidote for ARICEPT overdosage. Intravenous atropine sulfate titrated to effect is recommended: an initial dose of 1.0 to 2.0 mg IV with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics such as glycopyrrolate. It is not known whether ARICEPT and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration). Dose-related signs of toxicity in animals included reduced spontaneous movement, prone position, staggering gait, lacrimation, clonic convulsions, depressed respiration, salivation, miosis, tremors, fasciculation and lower body surface temperature. **NONCLINICAL TOXICOLOGY *Carcinogenesis, Mutagenesis, Impairment of Fertility:*** No evidence of a carcinogenic potential was obtained in an 88-week carcinogenicity study of donepezil hydrochloride conducted in CD-1 mice at doses up to 180 mg/kg/day (approximately 90 times the maximum recommended human dose on a mg/m^2 basis), or in a 104-week carcinogenicity study in Sprague-Dawley rats at doses up to 30 mg/kg/day (approximately 30 times the maximum recommended human dose on a mg/m^2 basis). Donepezil was not mutagenic in the Ames reverse mutation assay in bacteria, or in a mouse lymphoma forward mutation assay *in vitro*. In the chromosome aberration test in cultures of Chinese hamster lung (CHL) cells, some clastogenic effects were observed. Donepezil was not clastogenic in the *in vivo* mouse micronucleus test and was not genotoxic in an *in vivo* unscheduled DNA synthesis assay in rats. Donepezil had no effect on fertility in rats at doses up to 10 mg/kg/day (approximately 8 times the maximum recommended human dose on a mg/m^2 basis).

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