

Statins May Lower Risk of Dementia by 50%

BY MICHELE G. SULLIVAN

VIENNA — Statin treatment may reduce the risk of later dementia by more than 50%, a national Finnish study has determined.

“Disturbances in cholesterol metabolism have previously been linked to dementia development,” Dr. Alina Solomon wrote in a poster presented at the International Conference on

Alzheimer’s Disease. However, noted Dr. Solomon of the University of Kuopio, Finland, not all studies have concluded that statins confer a protective effect against dementia onset.

Dr. Solomon and her colleagues examined this question using data extracted from the national FINRISK study, a large, population-based survey of cardiovascular risk factors among Finnish citizens. The survey began in 1972 and is

conducted every 5 years. Dr. Solomon’s substudy of FINRISK included data on 17,257 citizens who were included in the 1997 and 2002 cohorts, and who were at least 60 years old in 1995, when statins became available in Finland.

By the study’s end at 2007, 1,551 of the subjects had developed dementia and 15,706 had not. Only 18% of those who developed dementia had taken at least 1 year of statin therapy, while 37% of

those who were dementia-free had taken a statin—a significant difference.

No significant associations were found between dementia and the use of other cholesterol-lowering medications, Dr. Solomon said, suggesting that “the effect of statins in dementia is partly independent of their cholesterol-lowering effect.”

Subjects who developed dementia also had significantly higher baseline total cholesterol and baseline systolic and diastolic blood pressure. But a multivariate regression model that controlled for age, gender, education, cholesterol, weight, and blood pressure still found that statins conferred a 57% risk reduction for dementia over the course of the study, Dr. Solomon said at the meeting, which was sponsored by the Alzheimer’s Association.

Neither she nor her coinvestigators declared any conflict of interest. ■

PTSD History May Warrant Dementia Screen

VIENNA — Posttraumatic stress disorder nearly doubled the risk of later dementia in large cohort of male veterans, a retrospective study has determined.

The finding points to the importance of close follow-up for veterans—or any patient—with symptoms of the stress-induced disorder, Dr. Kristine Yaffe said at the International Conference on Alzheimer’s disease. “It’s critical to follow patients with PTSD [posttraumatic stress disorder] and evaluate them early for dementia,” said Dr. Yaffe, director of the Memory Disorders Clinic at the San Francisco Veterans Administration Medical Center.

Dr. Yaffe studied the incidence of dementia in a retrospective cohort of 183,000 veterans in the Department of Veterans Affairs National Patient Care Database who did not have dementia at baseline enrollment (1997-2000). Most of the subjects (97%) were men; their mean age at baseline was 69 years. PTSD had been diagnosed in 53,155 of the subjects.

During a follow-up period from 2001 to 2007, the cumulative incidence of new-onset dementia was 11% for those veterans with PTSD and 7% for those without PTSD, a significant difference. The results did not change even when Dr. Yaffe excluded subjects with a history of traumatic brain injury, substance abuse, or depression. “Even after adjusting for demographics and medical and psychiatric comorbidities, PTSD patients in this study were still nearly twice as likely to develop incident dementia (hazard ratio 1.8) than veterans without PTSD,” she said at the meeting, which was sponsored by the Alzheimer’s Association.

Dr. Yaffe could not speculate on the nature of the connection between PTSD and dementia. She said she did not have any potential conflicts of interest with regard to the study.

—Michele G. Sullivan

humans at the maximum recommended human dose (MRHD) of 400 mg/day.

When lacosamide (25, 70, or 200 mg/kg/day) was orally administered to rats throughout gestation, parturition, and lactation, increased perinatal mortality and decreased body weights were observed in the offspring at the highest dose. The no-effect dose for pre- and post-natal developmental toxicity in rats (70 mg/kg/day) was associated with a maternal plasma lacosamide AUC approximately equal to that in humans at the MRHD.

Oral administration of lacosamide (30, 90, or 180 mg/kg/day) to rats during the neonatal and juvenile periods of postnatal development resulted in decreased brain weights and long-term neurobehavioral changes (altered open field performance, deficits in learning and memory). The early postnatal period in rats is generally thought to correspond to late pregnancy in humans in terms of brain development. The no-effect dose for developmental neurotoxicity in rats was associated with a plasma lacosamide AUC approximately 0.5 times that in humans at the MRHD.

Pregnancy Registry

UCB, Inc. has established the UCB AED Pregnancy Registry to advance scientific knowledge about safety and outcomes in pregnant women being treated with VIMPAT. To ensure broad program access and reach, either a healthcare provider or the patient can initiate enrollment in the UCB AED Pregnancy Registry by calling 1-888-537-7734 (toll free).

Physicians are also advised to recommend that pregnant patients taking VIMPAT enroll in the North American Antiepileptic Drug Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website <http://www.aedpregnancyregistry.org/>.

Labor and Delivery

The effects of VIMPAT on labor and delivery in pregnant women are unknown. In a pre- and post-natal study in rats, there was a tendency for prolonged gestation in all lacosamide treated groups at plasma exposures (AUC) at or below the plasma AUC in humans at the maximum recommended human dose of 400 mg/day.

Nursing Mothers

Studies in lactating rats have shown that lacosamide and/or its metabolites are excreted in milk. It is not known whether VIMPAT is excreted in human milk. Because many drugs are excreted into human milk, a decision should be made whether to discontinue nursing or to discontinue VIMPAT, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of VIMPAT in pediatric patients <17 years have not been established.

Lacosamide has been shown *in vitro* to interfere with the activity of CRMP-2, a protein involved in neuronal differentiation and control of axonal outgrowth. Potential adverse effects on CNS development can not be ruled out. Administration of lacosamide to rats during the neonatal and juvenile periods of postnatal development resulted in decreased brain weights and long-term neurobehavioral changes (altered open field performance, deficits in learning and memory). The no-effect dose for developmental neurotoxicity in rats was associated with a plasma lacosamide exposure (AUC) approximately 0.5 times the human plasma AUC at the maximum recommended human dose of 400 mg/day.

Geriatric Use

There were insufficient numbers of elderly patients enrolled in partial-onset seizure trials (n=18) to adequately assess the effectiveness of VIMPAT in this population.

In healthy subjects, the dose and body weight normalized pharmacokinetic parameters AUC and C_{max} were approximately 20% higher in elderly subjects compared to young subjects. The slightly higher lacosamide plasma concentrations in elderly subjects are possibly caused by differences in total body water (lean body weight) and age-associated decreased renal clearance. No VIMPAT dose adjustment based on age is considered necessary. Caution should be exercised for dose titration in elderly patients.

Patients with Renal Impairment

A maximum dose of 300 mg/day is recommended for patients with severe renal impairment (CL_{CR}≤30mL/min) and in patients with endstage renal disease. VIMPAT is effectively removed from plasma by hemodialysis. Following a 4-hour hemodialysis treatment, AUC of VIMPAT is reduced by approximately 50%.

Therefore dosage supplementation of up to 50% following hemodialysis should be considered. In all renal impaired patients, the dose titration should be performed with caution. [see *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)* in Full Prescribing Information]

Patients with Hepatic Impairment

Patients with mild to moderate hepatic impairment should be observed closely during dose titration. A maximum dose of 300 mg/day is recommended for patients with mild to moderate hepatic impairment. The pharmacokinetics of lacosamide has not been evaluated in severe hepatic impairment. VIMPAT use is not recommended in patients with severe hepatic impairment. [see *Dosage and Administration (2.3)* and *Clinical Pharmacology (12.3)* in Full Prescribing Information] Patients with co-existing hepatic and renal impairment should be monitored closely during dose titration.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

VIMPAT is a Schedule V controlled substance.

Abuse

In a human abuse potential study, single doses of 200 mg and 800 mg lacosamide produced euphoria-type subjective responses that differentiated statistically from placebo; at 800 mg, these euphoria-type responses were statistically indistinguishable from those produced by alprazolam, a Schedule IV drug. The duration of the euphoria-type responses following lacosamide was less than that following alprazolam. A high rate of euphoria was also reported as an adverse event in the human abuse potential study following single doses of 800 mg lacosamide (15% [5/34]) compared to placebo (0%) and in two pharmacokinetic studies following single and multiple doses of 300-800 mg lacosamide (ranging from 6% [2/33] to 25% [3/12]) compared to placebo (0%). However, the rate of euphoria reported as an adverse event in the VIMPAT development program at therapeutic doses was less than 1%.

Dependence

Abrupt termination of lacosamide in clinical trials with diabetic neuropathic pain patients produced no signs or symptoms that are associated with a withdrawal syndrome indicative of physical dependence. However, psychological dependence cannot be excluded due to the ability of lacosamide to produce euphoria-type adverse events in humans.

OVERDOSAGE

Signs, Symptoms, and Laboratory Findings of Acute Overdose in Humans

There is limited clinical experience with VIMPAT overdose in humans. The highest reported accidental overdose of VIMPAT during clinical development was 1200 mg/day which was non-fatal. The types of adverse events experienced by patients exposed to supratherapeutic doses during the trials were not clinically different from those of patients administered recommended doses of VIMPAT.

There has been a single case of intentional overdose by a patient who self-administered 12 grams VIMPAT along with large doses of zonisamide, topiramate, and gabapentin. The patient presented in a coma and was hospitalized. An EEG revealed epileptic waveforms. The patient recovered 2 days later.

Treatment or Management of Overdose

There is no specific antidote for overdose with VIMPAT. Standard decontamination procedures should be followed. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of patient. A Certified Poison Control Center should be contacted for up to date information on the management of overdose with VIMPAT.

Standard hemodialysis procedures result in significant clearance of VIMPAT (reduction of systemic exposure by 50% in 4 hours). Hemodialysis has not been performed in the few known cases of overdose, but may be indicated based on the patient’s clinical state or in patients with significant renal impairment.

PATIENT COUNSELING INFORMATION

See FDA-approved Medication Guide and Patient Counseling Information section in the Full Prescribing Information.

VIMPAT tablets and VIMPAT injection



Manufactured for
UCB, Inc.
Smyrna, GA 30080

VIMPAT® is a registered trademark under license from Harris FRC Corporation and covered by one or more claims of U.S. Patent 38,551.

© 2009 UCB, Inc. All rights reserved. Printed in U.S.A. • VE198-0309

1E 01/2009 UCB, Inc.

