Electronic Alerts Curb VTE in High-Risk Patients

BY BRUCE JANCIN Denver Bureau

NEW ORLEANS — An automated electronic alert program aimed at physicians responsible for high-risk patients not receiving prophylaxis against venous thromboembolism resulted in a substantial reduction in thromboembolic events in a large randomized trial, Nils Kucher, M.D., said at the annual scientific sessions of the American Heart Association.



Studies have shown that mechanical as well as pharmacologic prophylaxis against



Rx Only

Brief Summary of Prescribing Information.

For complete details, please see full Prescribing Information for NAMENDA. INDICATIONS AND USAGE

NAMENDA (memantine hydrochloride) is indicated for the treatment of moderate to severe dementia of the Alzheimer's type. CONTRAINDICATIONS

ne hydrochloride) is contraindicated in patients with known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation.

PRECAUTIONS

Information for Patients and Caregivers: Caregivers should be instructed in the recommended administration (twice per day for doses above 5 mg) and dose escalation (minimum interval of one week between dose increases)

Neurological Conditions Seizures: NAMENDA has not been systematically evaluated in patients with a seizure disorder. In clinical trials of NAMENDA, seizures occurred in 0.2% of patients treated with NAMENDA and 0.5% of patients treated with placebo

Genitourinary Conditions Conditions that raise urine pH may decrease the urinary elimination of memantine resulting in increased plasma levels of memantine.

Special Populations Hepatic Impairment

NAMENDA undergoes partial hepatic metabolism, but the major fraction of a dose (57-82%) is excreted unchanged in unine. The pharmacokinetics of memantine in patients with hepatic impairment have not been investigated, but would be expected to be only modestly affected. Renal Impairment

There are inadequate data available in patients with mild, moderate, and severe renal impairment but it is likely that patients with moderate renal impairment will have higher exposure than normal subjects. Dose reduction in these patients should be considered. The use of NAMENDA in patients with severe renal impairment is not recommended

Drug-Drug Interactions yl-D-aspartate (NMDA) antagonists: The combined use of NAMENDA with other NMDA antagonists (amantadine, ketamine, and dextromethorphan) has not been systematically evaluated and such use should be approached with caution.

Effects of NAMENDA on substrates of microsomal enzymes: In vitro studies conducted with marker substrates of CVP450 enzymes (CVP1A2, -2A6, -2C9, -2D6, -2E1, -3A4) showed minimal inhibition of these enzymes by memantine. No pharmacokinetic interactions with drugs metabolized by these enzymes are expected.

Here of inhibitors and/or substrates of microsomal enzymes on NAMENDA: Memantine is predominantly renally eliminated, and drugs that are substrates and/or inhibitors of the CYP450 system are not expected to alter the metabolism of memantine.

Acety/cholinesterase (AChE) inhibitors: Coadministration of NAMENDA with the AChE inhibitor donepezil HCI did not affect the pharmacokinetics of either compound. In a 24-week controlled clinical study in patients with moderate to severe Alzheimer's disease, the adverse event profile observed with a combination of memantine and donepezil was similar to that of donepezil alone.

Drugs eliminated via renal mechanisms: Because memantine is eliminated in part by tubular secretion, coadministration of drugs that use the same renal cationic system, including hydrochlorothiazide (HCTZ), triamterene (TA), cimetidine, ranitidine, quinidine, and nicotine, could potentially result in altered plasma levels of both agents. However ocadministration of NAMENDA and HCTZ/TA (id not affect the bioavailability of either memantine or TA, and the bioavailability of HCTZ decreased by 20% Drugs that make the urine alkaline: The clearance of memantine was reduced by about 80% under alkaline urine conditions at pH 8. Therefore alterations of urine pH towards the alkaline condition may lead to an accumulation of the drug with a possible increase in adverse effects. Urine pH is altered by diet, drugs (e.g. carbonic anhydrase inhibitors, sodium bicarbonate) and clinical state of the patient (e.g. renal tubular acidosis or severe infections of the urinary tract). Hence, used with caution under these conditions. memantine should be

Carcinogenesis, Mutagenesis and Impairment of Fertility There was no evidence of carcinogenicity in a 113-week oral study in mice at doses up to 40 mg/kg/day (10 times the maximum recommended human dose [MBHD] on a mg/m² basis). There was also no evidence of carcinogenicity in ratio rally dosed at up to 40 mg/kg/day for 71 weeks followed by 20 mg/kg/day (20 and 10 times the MRHD on a mg/m² basis, respectively) through 128 weeks.

Memantine produced no evidence of genotoxic potential when evaluated in the *in vitro* S. typhimurium or E. coli reverse mutation assay, an *in vitro* chromosomal aberration test in human lymphocytes, an *in vivo* cytogenetics assay for chromosome damage in rats, and the in vivo mouse micronucleus assay. The results were equivocal in an in vitro gene mutation assay using Chinese hamster V79 cells.

No impairment of fertility or reproductive performance was seen in rats administered up to 18 mg/kg/day (9 times the MRHD on a mg/m2 basis) orally from 14 days prior to mating through gestation and lactation in females, or for 60 days prior to mating in males.

Pregnancy

gnancy Category B: Memantine given orally to pregnant rats and pregnant rabbits during the period of organogenesis was not teratogenic up to the highest doses tested (18 mg/kg/day in rats and 30 mg/kg/day in rabbits, which are 9 and 30 times, respectively, the maximum recommended human dos e [MRHD] on a mg/m² basis). Slight maternal toxicity, decreased pup weights and an increased incidence

of nonossified cervical vertebrae were seen at an oral dose of 18 mg/kg/day in a study in which rats were given oral memantine beginning pre-mating and continuing through the postpartum period. Slight maternal toxicity and decreased pup weights were also seen at this dose in a study in which rats were treated from day 15 of gestation through the postpartum period. The no-effect dose for these effects was 6 mg/kg, which is 3 times the MRHD on a mg/m² basis. There are no adequate and well-controlled studies of memantine in pregnant

women. Memantine should be used during pregnancy only if the potentia benefit justifies the potential risk to the fetus. Nursing Mothers It is not known whether memantine is excreted in human breast milk

Because many drugs are excreted in human milk, caution should be exercised when me mantine is administered to a nursing mother Pediatric Use

There are no adequate and well-controlled trials documenting the safety and efficacy of memantine in any illness occurring in children ADVERSE REACTIONS

The experience described in this section derives from studies in patients with Alzheimer's disease and vascular dementia

Adverse Events Leading to Discontinuation: In placebo-controlled trials in which dementia patients received doses of NAMENDA up to 20 mg/day the likelihood of discontinuation because of an adverse event was the same in the NAMENDA group as in the placebo group. No individual adverse event was associated with the discontinuation of treatment in 1% r more of NAMENDA-treated patients and at a rate greater than placebo Adverse Events Reported in Controlled Trials: The reported adverse events in NAMENDA (memantine hydrochloride) trials reflect experience gained under closely monitored conditions in a highly selected patien population. In actual practice or in other clinical trials, these frequency mates may not apply, as the conditions of use, reporting behavior and the types of patients treated may differ Table 1 lists treatment-emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled dementia trials and for which the rate of occurrence was greater for patients treated with NAMENDA than for those treated with placebo. No adverse event occurred at a frequency of at least 5% and twice the placebo rate.

Table 1: Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving NAMENDA and at a Higher Frequency than Placebo-treated Patients

BODY System	Placebo	INAMENDA
Adverse Event	(N = 922)	(N = 940)
	%	%
Body as a Whole		
Fatigue	1	2
Pain	1	3
Cardiovascular System		
Hypertension	2	4
Central and Peripheral		
Nervous System		
Dizziness	5	7
Headache	3	6
Gastrointestinal System		
Constipation	3	5
Vomiting	2	3
Musculoskeletal System		
Back pain	2	3
Psychiatric Disorders		
Confusion	5	6
Somnolence	2	3
Hallucination	2	3
Respiratory System		
Coughing	3	4
Dyspnea	1	2

Other adverse events occurring with an incidence of at least 2% in NAMENDA-treated patients but at a greater or equal rate on placebo were agitation, fall, inflicted injury, urinary incontinence, diarrhea, bronchitis, insomnia, urinary tract infection, influenza-like symptoms, gait abnormal depression upper respiratory tract infection anxiety peripheral edema, nausea, anorexia, and arthralgia

The overall profile of adverse events and the incidence rates for individual adverse events in the subpopulation of patients with moderate to severe Alzheimer's disease were not different from the profile and incidence rates described above for the overall dementia population.

Vital Sign Changes: NAMENDA and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, diastolic blood pressure, and weight) and (2) the incidence of patients meeting criteria for potentially clinically significant changes for baseline in these variables. There were no clinically important changes in vital signs in patients treated with NAMENDA. A comparison of supine and standing vital sign measures for NAMENDA and placebo in elderly normal subjects indicated that NAMENDA treatment is not associated

Laboratory Changes: NAMENDA and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with NAMENDA treatment

ECG Changes: NAMENDA and placebo groups were compared with (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in ECG parameters associated with NAMENDA treatment.

Other Adverse Events Observed During Clinical Trials

NAMENDA has been administered to approximately 1350 patients with dementia, of whom more than 1200 received the maximum recommended dose of 20 mg/day. Patients received NAMENDA treatment for periods of

up to 884 days, with 862 patients receiving at least 24 weeks of treatment and 387 natients receiving 48 weeks or more of treatment Treatment emergent signs and symptoms that occurred during 8 controlled VTE is underutilized in at-risk patients.

In an effort to rectify this situation, Dr. Kucher and coworkers developed a computer program to electronically search the medical records of in-hospital patients and identify those at increased risk for VTE who weren't receiving prophylaxis.

The program sent an e-mail alert to the physician in charge of the patient's care that mentioned the full range of prophylactic options, such as compression stockings, low-molecular-weight heparin, un-

clinical trials and 4 open-label trials were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using WHO terminology, and event frequencies were calculated across all studies.

All adverse events occurring in at least two patients are included, except for those already listed in Table 1. WHO terms too general to be informative minor symptoms or events unlikely to be drug-caused, e.g., because they are common in the study population. Events are classified by body system 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 NAMENDA treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies

Body as a Whole: Frequent: syncope. Infrequent: hypothermia, allergic reaction

Cardiovascular System: Frequent: cardiac failure. Infrequent: angina pectoris, bradycardia, myocardial infarction, thrombophlebitis, atrial fibrillation, hypotension, cardiac arrest, postural hypote embolism, pulmonary edema

Central and Peripheral Nervous System: Frequent: transient ischemic attack, cerebrovascular accident, vertigo, ataxia, hypokinesia. Infrequent: paresthesia, convulsions, extrapyramidal disorder, hypertonia, tremor, aphasia, hypoesthesia, abnormal coordination, hemiplegia, hyperkinesia involuntary muscle contractions, stupor, cerebral he orrhage, neuralgia ptosis, neuropathy

Gastrointestinal System: Infrequent: gastroenteritis, diverticulitis ntestinal hemorrhage, melena, esophageal ulceratio

Hemic and Lymphatic Disorders: Frequent: anemia. Infrequent: leukopenia Metabolic and Nutritional Disorders: Frequent: increased alkaline phosphatase, decreased weight. Infrequent: dehydration, hyponatre aggravated diabetes mellitus.

Psychiatric Disorders: Frequent: aggressive reaction. Infrequent: delusion personality disorder, emotional lability, nervousness, sleep disorder, libido increased, psychosis, amnesia, apathy, paranoid reaction, thinking abnormal crving abnormal, appetite increased, paroniria, delirium, depersonalization neurosis, suicide attempt, Respiratory System: Frequent: pneumonia. Infrequent: apnea, asthma

hemoptysis Skin and Appendages: Frequent: rash. Infrequent: skin ulceration, pruritus,

cellulitis, eczema, dermatitis, ervthematous rash, alopecia, urticaria, Special Senses: Frequent: cataract, conjunctivitis. Infrequent: macula lutea degeneration, decreased visual acuity, decreased hearing, tinnitus blepharitis, blurred vision, corneal opacity, glaucoma, conjunctival hemorrhage, eye pain, retinal hemorrhage, xerophthalmia, diplopia, abnormal lacrimation, myopia, retinal detachment Urinary System: Frequent: frequent micturition. Infrequent: dysuria hematuria, urinary retention.

ADVERSE EVENTS FROM OTHER SOURCES

Memantine has been commercially available outside the United States since 1982, and has been evaluated in clinical trials including trials in patients with neuropathic pain, Parkinson's disease, organic brain syndrome, and spasticity. The following adverse events of possible importance for which there is inadequate data to determine the causal relationship have been reported to be temporally associated with memantine treatment in more than one patient and are not described elsewhere in labeling: acne bone fracture, carpal tunnel syndrome, claudication, hyperlipidemia impotence, otitis media, thrombocytopenia,

ANIMAL TOXICOLOGY

Memantine induced neuronal lesions (vacuolation and necrosis) in the multipolar and pyramidal cells in cortical layers III and IV of the posterior cingulate and retrosplenial neocortices in rats, similar to those which are known to occur in rodents administered other NMDA receptor antagonists. Lesions were seen after a single dose of memantine. In a study in which rats were given daily oral doses of memantine for 14 days, the no-effect have neuronal necrosis was 6 times the maximum recommended human dose on a mg/m² basis. The potential for induction of central neuronal vacuolation and necrosis by NMDA receptor antagonists in humans is unknown

DRUG ABUSE AND DEPENDENCE

bstance Class: Memantine HCl is not a controlled substance. Physical and Psychological Dependence: Memantine HCI is a low to moderate affinity uncompetitive NMDA antagonist that did not produce any evidence of drug-seeking behavior or withdrawal symptoms upon discontinuation in 2,504 patients who participated in clinical trials at therapeutic doses. Post marketing data, outside the U.S., retrospectively collected, has provided no evidence of drug abuse or depe

Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center to determine the As in any cases of overdose, general supportive measures should be utilized, and treatment should be symptomatic. Elimination of memantine can be enhanced by acidification of urine. In a documented case of an with up to 400 mg of memantine, the patient experienced restlessness, psychosis, visual hallucinations, somnolence, stupor and loss of consciousness. The patient recovered without permanent sequelae.

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fractionated heparin, and warfarin. The physician had to acknowledge the alert but could then choose to order or withhold prophylaxis.

The randomized trial involved 2,506 consecutive hospitalized patients at high risk for VTE who were not on prophylaxis. Physicians responsible for those in the intervention arm were issued an electronic alert. The alert was withheld from physicians caring for control patients.

Use of the computerized electronic alert program resulted in more than a doubling of orders for prophylaxis, from 14.5% in

The program searched the records of in-hospital patients and identified those at increased risk for VTE who weren't receiving prophylaxis.

the control group to 33.5% in the intervention group. The primary end point in the study was the overall VTE rate at 90 days, which was 4.9% in the intervention arm and 8.2% among the controls. This translated into a highly

significant 41% relative risk reduction. Pulmonary embolism was reduced by 60% in the intervention group, while proximal leg deep venous thromboembolism was decreased by 53%.

These benefits were achieved without an increase in major hemorrhage, which occurred in 1.5% of patients in both the intervention and control arms; 90-day mortality was 22% in each group as well.

The computer program identified patients as being at increased risk for VTE by using a scoring system that assigned 3 points each for prior VTE, cancer, or hypercoagulability; 2 points each for major surgery or a bed-rest order; and 1 point each for acute trauma, obesity, hormone therapy, or use of an OC. Patients with 4 or more points were defined as high-risk.

The reduction in VTE events seen with use of the electronic alert system was equally robust in patients with or without cancer, in both young and elderly patients, in men and women, and in those with or without a history of VTE.

Venous thromboembolism is said to be the No. 1 cause of unexpected in-hospital death. The annual incidence of VTE is 200,000-600,000 cases, resulting in up to 200,000 deaths.



'I'm ... worried that they are going to get "Pete's" isotretinoin, and it is not even going to have isotretinoin in it.'

> Dr. Hilary Baldwin, on the FDA's new restrictions on prescribing of isotretinoin, p. 22

OVERDOSAGE overdosage

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