Seasonal Flu Vaccine May Blunt H1N1 Severity

BY HEIDI SPLETE

WASHINGTON — The 2008 seasonal flu vaccine showed an overall vaccine effectiveness of 45% against infection with the pandemic influenza A(H1N1) virus in a study of military personnel conducted between April and October 2009, according to findings presented at the annual meeting of the American Society of Tropical Medicine and Hygiene.

This rate of vaccine effectiveness means that those vaccinated have a 45% lower chance of developing an infection, Dr. Jose Sanchez of the Armed Forces Health Surveillance Center in Silver Spring, Md., said in an interview. The confidence interval for the overall 45% seasonal vaccine effectiveness rate was 33%-55%.

Surprisingly, the greatest effectiveness was seen among individuals aged 17-24 years and in those aged 40 years and older, Dr. Sanchez said. Dr. Sanchez and colleagues conducted a case-control study of flu-related medical visits by active duty members of the U.S. military, compared with a control group of military individuals who presented with acute, nonrespiratory illness.

The study included 1,205 cases of H1N1 influenza and approximately four controls for each case.

Overall, 58% of the H1N1 cases occurred in individuals younger than age 25 years. After controlling for age, gender, and previous vaccination status, the seasonal flu vaccine effectiveness was 50% among those younger than 25 years, and 55% in those older than 39 years, Dr. Sanchez said. But there was no noticeable vaccine effectiveness among individuals aged 25-29 years (–6%) and an insignificant effect among those aged 30-39 years (9%).

In this military population, the live attenuated influenza vaccine (LAIV) and the trivalent inactivated vaccine (TIV) showed effectiveness of 22% and 35%, respectively. The effects of both types were significant, although the effectiveness of the LAIV just reached significance, Dr. Sanchez noted.

A total of 78 of the 1,205 H1N1 patients (6.5%) required hospitalization. The seasonal flu vaccination appeared to offer more protection against severe H1N1 disease, Dr. Sanchez said. The effectiveness of the seasonal flu vaccination was 62% among hospitalized patients, compared with 42% among outpatients.

The effectiveness of the seasonal flu vaccination against H1N1 was 62% among hospitalized patients, compared with 42% among outpatients.

Dr. Sanchez cited four previous studies of the impact of seasonal flu vaccine on H1N1 infection. Data from two studies suggested a protective effect, while data from two others, including a study from the Centers for Disease Control and Prevention, did not. "The increasing momentum of the H1N1 pandemic underscores the need for vaccination, yet there is a wide variance in vaccine effectiveness depending on the strain-match for a particular season," Dr. Sanchez said in a statement.

The U.S. military is a highly immunized population, and the results may not be applicable to civilian populations, Dr. Sanchez said. In addition, he suggested that a combination of natural influenza infections and prior influenza immunizations may contribute to "immunological priming" and create a cross-protective effect in active-duty military settings.

But he emphasized the importance of seasonal flu vaccination, even with the flood of attention being given to the H1N1 influenza virus. In an interview, he encouraged physicians not to forget about the seasonal flu vaccine, and to remind their patients to get vaccinated.

The military is in a unique position to monitor vaccine effectiveness in young and middle-aged adults, including groups of at-risk individuals that can be studied in randomized clinical trials, and data collection is ongoing, Dr. Sanchez said.

Dr. Sanchez had no financial conflicts to disclose. ■

effect, Intentional Injury, Retroperitoneal Fibrosis, Shock. Cardiovascular System – *Infrequent:* Deep thrombophlebitis, Heart failure, Hypotension, Postural hypotension, Retinal vascular disorder, Syncope; *Rare:* ST Depressed, Ventricular Fibrillation. Digestive System – *Frequent:* Gastroenteritis, Increased appetite; *Infrequent:* Cholecystitis, Cholelithiasis, Colitis, Dysphagia, Esophagitis, Gastritis, Gastrointestinal hemorrhage, Melena, Mouth ulceration, Pancreatitis, Rectal hemorrhage, Tongue edema; *Rare:* Aphthous stomatitis, Esophageal Ulcer, Periodontal abscess. Hemic and Lymphatic System – *Frequent:* Ecchymosis; *Infrequent:* Anemia, Eosinophilia, Hypochromic anemia, Leukocytosis, Leukopenia, Lymphadenopathy, Thrombocytopenia; *Rare:* Myelofibrosis, Polycythemia, Prothrombin decreased, Purpura, Thrombocythemia. Metabolic and Nutritional Disorders – *Rare:* Glucose Tolerance Decreased, Urate Crystalluria. Musculoskeletal System – *Frequent:* Arthralgia, Leg cramps, Myalgia, Myasthenia; *Infrequent:* Arthrosis; *Rare:* Chondrodystrophy, Generalized Spasm. Nervous System – *Frequent:* Anxiety, Depersonalization, Hypertonia, Hypesthesia, Libido decreased, Nystagmus, Paresthesia, Stupor, Twitching; *Infrequent:* Abnormal dreams, Agitation, Apathy, Aphasia, Circumoral paresthesia, Dysarthria, Hallucinations, Hostility, Hyperalgesia, Hyperesthesia, Hyperkinesia, Hypokinesia, Hypotonia, Libido increased, Myoclonus, Neuralgia; *Rare:* Addiction, Cerebellar syndrome, Cogwheel rigidity, Coma, Delirium, Delusions, Dysautonomia, Dyskinesia, Dystonia, Encephalopathy, Extrapyramidal syndrome, Guillain-Barré syndrome, Hypalgesia, Intracranial hypertension, Manic reaction, Paranoid reaction, Peripheral neuritis, Personality disorder, Psychotic depression, Schizophrenic reaction, Sleep disorder, Torticollis, Trismus. Respiratory System – *Rare:* Apnea, Atelectasis, Bronchiolitis, Hiccup, Laryngismus, Lung edema, Lung fibrosis, Yawn. Skin and Appendages – *Frequent:* Pruritus; *Infrequent:* Alopecia, Dry skin, Eczema, Hirsutism, Skin ulcer, Urticaria, Vesiculobullous rash; *Rare:* Angioedema, Exfoliative dermatitis, Lichenoid dermatitis, Melanosis, Nail Disorder, Petechial rash, Purpuric rash, Pustular rash, Skin atrophy, Skin necrosis, Skin nodule, Stevens-Johnson syndrome, Subcutaneous nodule. Special senses – *Frequent:* Conjunctivitis, Diplopia, Otitis media, Tinnitus; *Infrequent:* Abnormality of accommodation, Blepharitis, Dry eyes, Eye hemorrhage, Hyperacusis, Photophobia, Retinal edema, Taste loss, Taste perversion; *Rare:* Anisocoria, Blindness, Corneal ulcer, Exophthalmos, Extraocular palsy, Iritis, Keratitis, Keratoconjunctivitis, Miosis, Mydriasis, Night blindness, Ophthalmoplegia, Optic atrophy, Papilledema, Parosmia, Ptosis, Uveitis. Urogenital System – *Frequent:* Anorgasmia, Impotence, Urinary frequency, Urinary incontinence; *Infrequent:* Abnormal ejaculation, Albuminuria, Amenorrhea, Dysmenorrhea, Dysuria, Hematuria, Kidney calculus, Leukorrhea, Menorrhagia, Metrorrhagia, Nephritis, Oliguria, Urinary retention, Urine abnormality; *Rare:* Acute kidney failure, Balanitis, Bladder Neoplasm, Cervicitis, Dyspareunia, Epididymitis, Female lactation, Glomerulitis, Ovarian disorder, Pyelonephritis.

Comparison of Gender and Race The overall adverse event profile of pregabalin was similar between women and men. There are insufficient data to support a statement regarding the distribution of adverse experience reports by race.

Post-marketing Experience The following adverse reactions have been identified during postapproval use of LYRICA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Nervous System Disorders – Headache. Gastrointestinal Disorders – Nausea, Diarrhea.

DRUG INTERACTIONS

Since LYRICA is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), and does not bind to plasma proteins, its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions or protein binding displacement. *In vitro* and *in vivo* studies showed that LYRICA is unlikely to be involved in significant pharmacokinetic drug interactions. Specifically, there are no pharmacokinetic interactions between pregabalin and the following antiepileptic drugs: carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, and topiramate. Important pharmacokinetic interactions would also not be expected to occur between LYRICA and commonly used antiepileptic drugs. **Pharmacodynamics** Multiple oral doses of LYRICA were co-administered with oxycodone, lorazepam, or ethanol. Although no pharmacokinetic interactions were seen, additive effects on cognitive and gross motor functioning were seen when LYRICA was co-administered with these drugs. No clinically important effects on respiration were seen.

USE IN SPECIFIC POPULATIONS

Pregnancy Pregnancy Category C. Increased incidences of fetal structural abnormalities and other manifestations of developmental toxicity, including lethality, growth retardation, and nervous and reproductive system functional impairment, were observed in the offspring of rats and rabbits given pregabalin during pregnancy, at doses that produced plasma pregabalin exposures (AUC) ≥5 times human exposure at the maximum recommended dose (MRD) of 600 mg/day. When pregnant rats were given pregabalin (500, 1250, or 2500 mg/kg) orally throughout the period of organogenesis, incidences of specific skull alterations attributed to abnormally advanced ossification (premature fusion of the jugal and nasal sutures) were increased at ≥1250 mg/kg, and incidences of skeletal variations and retarded ossification were increased at all doses. Fetal body weights were decreased at the highest dose. The low dose in this study was associated with a plasma exposure (AUC) approximately 17 times human exposure at the MRD of 600 mg/day. A no-effect dose for rat embryo-fetal developmental toxicity was not established. When pregnant rabbits were given LYRICA (250, 500, or 1250 mg/kg) orally throughout the period of organogenesis, decreased fetal body weight and increased incidences of skeletal malformations, visceral variations, and retarded ossification were observed at the highest dose. The no-effect dose for developmental toxicity in rabbits (500 mg/kg) was associated with a plasma exposure approximately 16 times human exposure at the MRD. In a study in which female rats were dosed with LYRICA (50, 100, 250, 1250, or 2500 mg/kg) throughout gestation and lactation, offspring growth was reduced at ≥100 mg/kg and offspring survival was decreased at ≥250 mg/kg. The effect on offspring survival was pronounced at doses ≥1250 mg/kg, with 100% mortality in high-dose litters. When offspring were tested as adults, neurobehavioral abnormalities (decreased auditory startle responding) were observed at ≥250 mg/kg and reproductive impairment (decreased fertility and litter size) was seen at 1250 mg/kg. The no-effect dose for pre- and postnatal developmental toxicity in rats (50 mg/kg) produced a plasma exposure approximately 2 times human exposure at the MRD. There are no adequate and well-controlled studies in pregnant women. LYRICA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. To provide information regarding the effects of in utero exposure to LYRICA, physicians are advised to recommend that pregnant patients taking LYRICA enroll in the North American Antiepileptic Drug (NAAED) 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 LYRICA on labor and delivery in pregnant women are unknown. In the prenatal-postnatal study in rats, pregabalin prolonged gestation and induced dystocia at exposures ≥50 times the mean human exposure ($AUC_{(0-24)}$ of 123 µg•hr/mL) at the maximum recommended clinical dose of 600 mg/day. **Nursing Mothers** It is not known if pregabalin is excreted in human milk; it is, however, present in the milk of rats. Because many drugs are excreted in human milk, and because of the potential for tumorigenicity shown for pregabalin in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use** The safety and efficacy of pregabalin in pediatric patients have not been established. In studies in which pregabalin (50 to 500 mg/kg) was orally administered to young rats from early in the postnatal period (Postnatal Day 7) through sexual maturity, neurobehavioral abnormalities (deficits in learning and memory, altered locomotor activity, decreased auditory startle responding and habituation) and reproductive impairment (delayed sexual maturation and decreased fertility in males and females) were observed at doses ≥50 mg/kg. The neurobehavioral changes of acoustic startle persisted at ≥250 mg/kg and locomotor activity and water maze performance at ≥500 mg/kg in animals tested after cessation of dosing and, thus, were considered to represent long-term effects. The low effect dose for developmental neurotoxicity and reproductive impairment in juvenile rats (50 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately equal to human exposure at the maximum recommended dose of 600 mg/day. A no-effect dose was not established. **Geriatric Use** In controlled clinical studies of LYRICA in fibromyalgia, 106 patients were 65 years of age or older. Although the adverse reaction profile was similar between the two age groups, the following neurological adverse reactions were more frequent in patients 65 years of age or older: dizziness, vision blurred, balance disorder, tremor, confusional state, coordination abnormal, and lethargy. LYRICA is known to be substantially excreted by the kidney, and the risk of toxic reactions to LYRICA may be greater in patients with impaired renal function. Because LYRICA is eliminated primarily by renal excretion, the dose should be adjusted for elderly patients with renal impairment.

DRUG ABUSE AND DEPENDENCE

Controlled Substance LYRICA is a Schedule V controlled substance. LYRICA is not known to be active at receptor sites associated with drugs of abuse. As with any CNS active drug, physicians should carefully evaluate patients for history of drug abuse and observe them for signs of LYRICA misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behavior). **Abuse** In a study of recreational users (N=15) of sedative/hypnotic drugs, including alcohol, LYRICA (450 mg, single dose) received subjective ratings of "good drug effect," "high" and "liking" to a degree that was similar to diazepam (30 mg, single dose). In controlled clinical studies in over 5500 patients, 4% of LYRICA-treated patients and 1% of placebo-treated patients overall reported euphoria as an adverse reaction, though in some patient populations studied, this reporting rate was higher and ranged from 1 to 12%. **Dependence** In clinical studies, following abrupt or rapid discontinuation of LYRICA, some patients reported symptoms including insomnia, nausea, headache or diarrhea *[see Warnings and Precautions]*, suggestive of physical dependence.

OVERDOSAGE

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans There is limited experience with overdose of LYRICA. The highest reported accidental overdose of LYRICA during the clinical development program was 8000 mg, and there were no notable clinical consequences. In clinical studies, some patients took as much as 2400 mg/day. The types of adverse reactions experienced by patients exposed to higher doses (≥900 mg) were not clinically different from those of patients administered recommended doses of LYRICA. Treatment or Management of Overdose There is no specific antidote for overdose with LYRICA. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; usual precautions should be observed to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. A Certified Poison Control Center should be contacted for up-to-date information on the management of overdose with LYRICA. Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment. Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours).

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenesis A dose-dependent increase in the incidence of malignant vascular tumors (hemangiosarcomas) was observed in two strains of mice (B6C3F1 and CD-1) given pregabalin (200, 1000, or 5000 mg/kg) in the diet for two years. Plasma pregabalin exposure (AUC) in mice receiving the lowest dose that increased hemangiosarcomas was approximately equal to the human exposure at the maximum recommended dose (MRD) of 600 mg/day. A no-effect dose for induction of hemangiosarcomas in mice was not established. No evidence of carcinogenicity was seen in two studies in Wistar rats following dietary administration of pregabalin for two years at doses (50, 150, or 450 mg/kg in males and 100, 300, or 900 mg/kg in females) that were associated with plasma exposures in males and females up to approximately 14 and 24 times, respectively, human exposure at the MRD. Mutagenesis Pregabalin was not mutagenic in bacteria or in mammalian cells *in vitro*, was not clastogenic in mammalian systems *in vitro* and *in vivo*, and did not induce unscheduled DNA synthesis in mouse or rat hepatocytes. Impairment of Fertility In fertility studies in which male rats were orally administered pregabalin (50 to 2500 mg/kg) prior to and during mating with untreated females, a number of adverse reproductive and developmental effects were observed. These included decreased sperm counts and sperm motility, increased sperm abnormalities, reduced fertility, increased preimplantation embryo loss, decreased litter size, decreased fetal body weights, and an increased incidence of fetal abnormalities. Effects on sperm and fertility parameters were reversible in studies of this duration (3–4 months). The no-effect dose for male reproductive toxicity in these studies (100 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately 3 times human exposure at the maximum recommended dose (MRD) of 600 mg/day. In addition, adverse reactions on reproductive organ (testes, epididymides) histopathology were observed in male rats exposed to pregabalin (500 to 1250 mg/kg) in general toxicology studies of four weeks or greater duration. The no-effect dose for male reproductive organ histopathology in rats (250 mg/kg) was associated with a plasma exposure approximately 8 times human exposure at the MRD. In a fertility study in which female rats were given pregabalin (500, 1250, or 2500 mg/kg) orally prior to and during mating and early gestation, disrupted estrous cyclicity and an increased number of days to mating were seen at all doses, and embryolethality occurred at the highest dose. The low dose in this study produced a plasma exposure approximately 9 times that in humans receiving the MRD. A no-effect dose for female reproductive toxicity in rats was not established. Human Data In a double-blind, placebo-controlled clinical trial to assess the effect of pregabalin on sperm motility, 30 healthy male subjects were exposed to pregabalin at a dose of 600 mg/day. After 3 months of treatment (one complete sperm cycle), the difference between placebo- and pregabalin-treated subjects in mean percent sperm with normal motility was <4% and neither group had a mean change from baseline of more than 2%. Effects on other male reproductive parameters in humans have not been adequately studied.

Animal Toxicology and/or Pharmacology Dermatopathy Skin lesions ranging from erythema to necrosis were seen in repeated-dose toxicology studies in both rats and monkeys. The etiology of these skin lesions is unknown. At the maximum recommended human dose (MRD) of 600 mg/day, there is a 2-fold safety margin for the dermatological lesions. The more severe dermatopathies involving necrosis were associated with pregabalin exposures (as expressed by plasma AUCs) of approximately 3 to 8 times those achieved in humans given the MRD. No increase in incidence of skin lesions was observed in clinical studies. Ocular Lesions Ocular lesions (characterized by retinal atrophy [including loss of photoreceptor cells] and/or corneal inflammation/mineralization) were observed in two lifetime carcinogenicity studies in Wistar rats. These findings were observed at plasma pregabalin exposures (AUC) ≥2 times those achieved in humans given the maximum recommended dose of 600 mg/day. A no-effect dose for ocular lesions was not established. Similar lesions were not observed in lifetime carcinogenicity studies in two strains of mice or in monkeys treated for 1 year.

Distributed by:

Parke-Davis
Division of Pfizer Inc
New York, NY 10017

PBP00681B

Revised November 2009

© 2009 Pfizer Inc.

All rights reserved.

LYRICA® PREGABALIN C capsules

Working together for a healthier world™