Angioedema Risk Up in Blacks on ACE Inhibitors

BY MITCHEL L. ZOLER Philadelphia Bureau

ORLANDO, FLA. — About 2% of African Americans treated with an ACE inhibitor develop angioedema within the first 6 months on the drug, according to results from a prospective study of enalapril with more than 12,000 patients.

Although angioedema is a known potential adverse effect of treatment with an ACE inhibitor, prior findings never established the risk patients face in a prospective, controlled study, John B. Kostis, M.D., said while presenting a poster at the annual meeting of the American College of Cardiology. Among whites in the study, about 0.5% developed angioedema during the first 6 months of treatment with enalapril.

Patients who developed angioedema most commonly had it soon after starting enalapril, but the results also showed that the adverse effect could occur at any time, especially in African Americans. A time

r dysfunction, those taking diuretics and ACE teroidal anti-inflammatory drug therapy is u ate.

cause this prolonged bleeding effect may be exagg tic defects, Combunox should be used with caution in

plot of the appearance of angioedema in African Americans showed an increasing cumulative incidence throughout the 6 months of treatment. For example, about 1% of these patients developed angioedema within the first 40 days on enalapril, and another 0.5% had the effect during the next 30 days. During the final 110 days of the study, another 0.5% were affected. In contrast, virtually all white patients who developed angioedema had their reaction within the first 70 days of treatment.

tects in the nursing infant have not been documented, withdrawal can occur in breast-feeding ants when maternal administration of an opioid analgesic is discontinued. cause of the potential for serious adverse reactions in nursing infants from the oxycodone serint in combune, a decision should be made whether to discontinue nursing or to discon-ule the drug, taking into account the importance of the drug to the mother. **distric Use**

anny and clinical studies of pain following dental surgery, 109 pati nd 17 years were administered a single dose of Combunox. No ap ad in the safety of Combunox in patients below and above 17 y not been studied in patients under 14 years of age.

Ise number of subjects in clinical studies of Combunox, 89 patients were 65 and over, atients were 75 and over. No overall differences in safety were observed between ects and younger subjects, and other reported clinical experience has not identified in responses between the elderly and younger patients, but greater sensitivity of individuals cannot be ruled out. ecause the elderly may be more sensitive to the renal and gastrointestinal effects of al anti-inflammatory agents as well as possible increased risk of respiratory depres-middle weather the elderly with Combunov.

ADVERSE REACTIONS

erse event information is also pro nbunox in a multiple dose analge ns, given up to four times daily fo rse Events Which Occurred at a Frequency of ≥ 1% and at a Higher Ind the Placebo Group in Single Dose Studies

| and the store and provide a store statutes | | | | |
|--|---------------------|--------------------------------|----------------------------------|--------------------|
| | 5/400 mg (n=923) | 400 mg Ibuprofen (n=913) | 5 mg Oxycodone HCI (n=286) | Placebo (n=315) |
| Digestive | | | | |
| Nausea | 81 (8.8%) | 44 (4.8%) | 46 (16.1%) | 21 (6.7%) |
| Vomiting | 49 (5.3%) | 16 (1.8%) | 30 (10.5%) | 10 (3.2%) |
| Flatulence | 9 (1.0%) | 7 (0.8%) | 3 (1.0%) | 0 |
| Nervous System | | | | |
| Somnolence | 67 (7.3%) | 38 (4.2%) | 12 (4.2%) | 7 (2.2%) |
| Dizziness | 47 (5.1%) | 21 (2.3%) | 17 (5.9%) | 8 (2.5%) |

 kin and Appendages

 weat
 15 (1.6%)
 7 (0.8%)
 4 (1.4%)
1 (0.3%) that were reported by at least 1% of patients taking Combunox bu dence in the placebo treated patients were fever, headache and p that occurred in less than 1% and in at least two Combunox tr udies not listed above include the following: **Body as Whole:** pain, enlarged abdomen. **Cardiovascular System:** hypotension,

llowing: Body as Wh Digest Alton. Organization of the second sec

asodilation (3.0%). Digestive System: nausea (25.4%), vomiting (4.5%). Ne lar System: vasodilation (3.0%). Digesuve systems epsia (2.1%), nausea (25.4%), vomiting (4.5% lence (17.4%). ccurred in less than 2% of and at least two Cor

entis that occurred in tess that 2% of allot at tess two combolino is Dose study on listed previously include the following: Body as ction. Cardiovascular System: thrombophlebitis. Hemic and L s. Metabolic and Nutritional Disorders: hypokalemia. Muscul iervous System: abnormal thinking, axvide, hypokrinsia, hyp as: rash. Special Senses: amblyopia, taste perversion. Urogenit

RUG ABUSE AND DEPENDENCE

x contains oxycodone, which is a mu-opioid agonist with an a id agonists and is a Schedule II control substance. Combu algesia, can be abused and are subject to criminal diversion. is a primary, chronic, neurobiologic disease, with genetic, psy tors influencing its development and manifestations. It is cha e one or more of the following, impaired control over drug us despite harm and control.

acrors munencing its everyopment and manifestations. It is characteriza due one or more of the following: impaired control over drug use, comp se despite harm, and craving. Drug addiction is a treatable disease util approach, but refapes is common existing "behavior is very common in addicts and drug abuers. Drug amergency calls or visits near the end of difice hours, refusal to unde tion, testing or referal, repeated "loss" of prescriptions, tampering wit cance to provide prior medical records or contact information for other "Doctor stopping" to obtain additional prescriptions is common amon be suffering from untreated addiction. It addiction are separate and distinct from physical dependence and tok not usually assume sclinically sitemificant dimensions after serveral dr

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physical dependence usually assumes clinically significant dimensions after several days to weeks of continuous opioid use. Tolerance, in which increasingly large doesa are required in order to pro-duce the same degree of analgesia, is manifested initially by a shorter duration of analgesic effect, and subsequently by a decrease in the intensity of analgesia. The rate of development of tolerance varies among patients. Physicians should be avare that abuse of opioids can occur in combination with other psychoactive substances. Combunox, like other opioids, may be diverted for non-medical use. Record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised. Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of the page. Jency, per assessm rapy, and pro mioid drugs.

ng an acute overdosage, toxicity may result from oxycodone and/or ibun

rdosage with oxycodone may be manifested by respiratory depre-ng to stupor or coma, skeletal muscle flaccidity, cold and clamm

word trom oxycodone a public broken of the second second second second second public broken overdose is dependent on the amount of drug leased since ingestion, although individual response may vary, necess ation of each case. Although uncommon, serious toxicity and death has medical literature with bluproten overdosage. The most frequently i bluproten overdose include abdominal pain, nausea, vomiting, lettargy, ardiavascular toxicity, including hypotension, braken-varianest.

isopressors) should be employed ema accompanying overdose, as massage or defibrillation. The nard ministerid as needed to maintain adequate respiration s and gastrointestinal bleeding may be necessary. In c uld be emptied through ipecac-induced emesis or gas d charcoal may help in reducing the absorption and st effective if initiated within 30 minutes of ingestion. I patients with impaired conscioueness or overdoes gr nponent in children because of the risk for convulsione is contents

Forest Pharmaceuticals, Inc.

11/04 © 2004 Forest Laboratories Inc

This analysis used data collected in a 25,000-patient study that compared the drugs omapatrilat and enalapril in patients with hypertension. Randomization assigned 12,634 patients to treatment with enalapril, of whom about 10% were African American. Patients were allowed to have a history of treatment with an ACE inhibitor, and 35% of enrolled patients had this background.

Dosages of both drugs were titrated during the first 8 weeks so that blood pressures were below 140/90 mm Hg. During the subsequent 16 weeks, adjunctive antihypertensive therapy could be added to help patients reach or maintain the target blood pressure.

African Americans had a 2.9-fold increase in risk, compared with whites. A history of seasonal allergies and age over 65 years also raised risk.

Overall, angioedema developed in 86 (0.7%) of the patients treated with enalapril, reported Dr. Kostis, chairman of the department of medicine at the Robert Wood Johnson University Hospital in New Brunswick, N.J.

Most patients' first symptom of angioedema is lip swelling. All patients had been instructed at the start of treatment to immediately stop their medication and contact their physician if this or other symptoms of angioedema occurred.

Among the 86 patients with angioedema in the study, 65 (75%) had the mildest form, class I, which required no special treatment aside from stopping enalapril. A class II reaction occurred in 19 (22%) patients, requiring treatment with catecholamines or steroids. Two patients (2%) had a class IIIa reaction that required hospitalization but without airway compromise. No patients had the most severe form of angioedema, class IV, which means that either airway protection is needed or that the patient dies.

A step-wise logistic regression analysis was done using several candidate demographic and clinical variables to calculate the risk contributed by individual factors. The strongest risk factor was a history of rash in response to drugs, which boosted the risk of angioedema 3.8-fold.

African Americans had a 2.9-fold increased risk, compared with white patients. The other significant risk factors were a history of seasonal allergies, which raised risk by 79%, and age greater than 65 years, which boosted risk by 60%.

It's unclear why ACE inhibitors cause angioedema. The most commonly proposed hypothesis is that the effect stems from their inhibition of the breakdown of bradykinin, which then accumulates. The swelling seen in angioedema resembles what happens in patients with a C1 inhibitor deficiency, which is known to be caused by excess bradykinin production, said Harold J. Kim, M.D., a cardiologist at Robert Wood Johnson University Hospital and a collaborator on this study.

Combunox> (Oxycodone HCI and Ibuprofen) Tablets 5 mg/400 mg

FOREST LABORATORIES Brief Summary: For complete details, please see full prescribing information for Combunox. NIDICATIONS AND USAGE Combunox tablets are indicated for the short term (no more than 7 days) management of acute, moderate to severe pain.

ICATIONS

DICATIONS should not be administered to patients who have previously exhibited hyper done HCI, buprofen, or any of Combunox's components, or in any situatio contraindicated. This includes patients with significant respiratory depres d settings or the absence of resuscitative equipment) and patients with hchial asthma or hyperachia. Combunox should not be given to patient with d of having paralytic ileus. Combunox should not be given to patient with hna, urticaria, or allergici-type reactions after taking apprin or other NSADB joid reactions to NSAIDs, some of which were fatal, have been reported wARNINGS - Kanphydactiot Reactions, and PERCAUTIONS - Pre-existing / own to be hypersensitive to other opiolds may exhibit cross-sensitivity to oxy

WARNINGS Misuse Abuse and Diversion of Opioids Comburox contains oxycodone, which is an opioid agonist, and a Schedule II controlled substance. Opioid agonists have the potential for being abused and are sought by abusers and people with addiction disorders, and are subject to diversion. Comburox can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing Comburox on isituations where the physi-cian or pharmacost is concerned about an increased risk of misuse, abuse or diversion (see DRUG ABUSE AND DEFENDENCE). Benization: Demossion

a AbuSe And Det enderson, indery Depression dose-related respiratory depression by acting directly on the b respiratory centers. Oxycodone HCI also affects the center that controls respira m, and may produce irregular and periodic breathing. Respiratory depression occurs n ently in elderly or debilitated patients, usually following large initial does in non-tolen rits, or when opioids are given in conjunction with other agents that depress respirat burox should be used with externe caution in patients with significant chronic obstru-ruonary disease or cor pulmonale, and in patients having substantially decreased respirat ver, hypoxa, hypercarphia, or pre-existing respiratory depression. In such patients, it hereixperitie coses of Combunox may decrease respiratory drive to the point of apne tanesia.

tensive Effect maintain blood pressure has been compromised by a depleted blood volume, or after con maintain blood pressure has been compromised by a depleted blood volume, or after con in daministration with drugs such as phenothazines or other agents which compromise motor tone. Combunox may produce orthostatic hypotension in ambulatory patients bunox, like all opioid analgesics, should be administered with caution to patients incident cardination of the such as the such a

sure: y and increased intracranial Pressure ratory depressant effects of opioids and their capacity to elevate cereb may be markedly exaggerated in the presence of head injury, intracrania g increase in intracranial pressure. Furthermore, opioids produce adve obscure the clinical course of patients with head injuries.

ons bids may obscure the diagnosis or clinical course of patients with acute

Effects Tinestine or large intestine, can occur at any time, with or without intestine or large intestine, can occur at any time, with or without nts treated with non-steroidal anti-inflammatory drugs (NSAIDs) per GI problems, such as dyspepsia, are common and may also occ heapy. Therefore, physicians and patients should remain altert for u the absence of previous GI tract symptoms. Even short term thera

uld be prescribed with extreme caution in those with a prior history of ulcer dis stinal bleeding. Most spontaneous reports of tala GI events are in elerety or of is and, therefore, special care should be taken in treating this population. To netmal risk for an adverse GI event the treatment period should be of the sho ration. For high risk patients, attemate therapies that do not involve NSAIDs sh

n to a past history of ulcer disease, pharmacoepidemiological studies have ide

Reactions reactions may occur in patients without known prior exposure juid not be qiven to patients with the aspirin triad or a history of an curs in asthmatic patients who experience rhinitis with or withou severe, potentially fatal bronchospasm after taking aspirin or other SAIDs have been reported in such patients (see CONTRAIND or Pre-existing Asthma). Emergency help should be sought when

Tion occurs. anced Renal Disease addents with advanced kidney disease, treatment with Combunox is not addents with advanced kidney timister in the NSAID component, of the patient's kidney function is advisable (see PRECAUTIONS - Renal Effe onancy

Pregnancy As with other NSAID-containing products, Combunox should be avoided in late pregnancy because it may cause premature closure of the ductus arteriosus. Interactions with Alcohol and Drugs of Abuse Oxycodone may be expected to have additive affects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

Rick Patie

ms, anu ruose wm severe impairment of hepatic, pulmonary or renal 1, Addison's disease, acute alcoholism, convulsive disorders, CNS depre tremens, kyphoscollosis associated with respiratory depression, to chypetrophy or urethral stricture. The usual precautions should be o lify of respiratory depression, construial hondnenics and albed center of the stricture of the stricture.

n mind. ic/Biliary Tract Disease i cause spasm of the sphin iliary tract disease, includin in the serum amylase level. ncter of Oddi and should be used with car or acute pancreatitis. Opioids like Combun

ses the cough reflex; as with other opioid containing products, caution Combunox is used postoperatively and in patients with pulmonary dis

A Witell Control to use a personal approximation and a second and anti-inflammatory activity of ibuprofen may reduce fever and inflammation shing their utility as diagnostic signs in detecting complications of presumed nonin-

NSAIDs, ibuprofen has been reported to cause borderline ele mes; this may occur in up to 15% of patients. These abnormali tially unchanged, or may be transient with continued therapy. In ormal elevations of SGPT (ALT) or SGOT (AST) occurred in than 1% of patients. A patient with symptoms and/or signs s whom an abnormal liver test has occurred, should be evaluat in of more severe henatic reactions while on therapy with Coninical signs and symptoms consistent with liver disease deve occur (e.g. eosinophilia, rash, etc.), Combunox should be dis

Id be used when initiating treatment with Combunox in patients with (

recommension in parameters in the parameters in nges. Renal toxicity has also been seen ir ensatory role in the maintenance of renal p steroidal anti-inflammatory drug may cau nation and, secondarily, in renal blood flow

n defects and those on anticoagulant t g NSAIDs, including ibuprofen. This ma ition and edema have been reported in association with ibuprofen; therefore, the drug used with caution in patients with a history of cardiac decompensation. hypertension

fects her NSAIDs, can inhibit platelet aggregation but the retion than that seen with asnirin. Ibuprofen has be

Meningitis reeningitis with fever and coma has been observed on rare occasions in pa en therapy. Although it is probably more likely to occur in patients with system ratosus and related connective tissue diseases, it has been reported in patients e an underlying chronic disease. It disno so symptoms of meningitis develop in humox, the possibility of its being related to ibuprofen should be considered. The provide the performance of potentially hazardous tasks such as driving a car or proteints.

nts should be cautioned accordingly. oduct with alcohol and other CNS depressants may produce an addi-

combination of this product with alcohol and other CNS depressants may produce an addi-to CNS depression and should be avoided. Inbunox can be abused in a manner similar to other opioid agonists, legal or illicit. Patients yuld take the drug only for as long as it is prescribed, in the amounts prescribed, and no more useful then prescribed.

nan preserved. like other drugs containing ibuprofen, is not free of side effects. The side effects of can cause discomfort and, rarely, there are more serious side effects, such as gasdrugs can cause discontort and, rarely, there are more serious side effects, su testinal heading, which may result in hospitalization and even fatal outcome id be instruded to report any signs or symptoms of gastrointestinal bleeding, blu here eye problems, skin rash, weight gain, or edema. ratory Testina and the series of the serie

ne ne is metabolized in part to oxymorphone via the cytochrome P_{sic} isoenzyme CYP2D6. is pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs and essantis), such blockade has not yet been shown to be of cinical significance with this owever, clinicians should be avare of this possible interaction. Inergics: The concurrent use of anticholinergics with oxycodone preparations may pro-radio-lineur

agent. However, clinicians should be aware of this possible interaction. Anticholinergics well and constraints well and the state of t

opping such treatment. omuscular Blocking Agents: Oxycodone, as well as other opioid analgesics, may enhance reuromuscular blocking action of skeletal muscle relaxants and produce an increased ee of respiratory depression.

ors: Reports suggest that NSAIDs may diminish the antihypertensions. This interaction should be given consideration in patients taking

oncomitantly with ACE-inhibitors. spirin: As with other products containing NSAIDs, concomitant administration of Comi d aspirin is no generally recommended because of the potential of increased adverse e juretics: Ibuproten has been shown to reduce the natriuretic effect of furosemide and this

buppofen has been shown to reduce the nativuetic effect of furces apatients. This response has been attributed to inhibition of renal pring oncomitant therapy with Combunox the patient should be o renal failure (see PRECAUTIONS - Renal Effects), as well as diuret bluprofen has been shown to elevate plasma lithium concentratia learance. This effect has been attributed to inhibition of renal pro-fen. Thus, when combunox and lithium are administered concurre

ofen. Thus, when Computors and human are administered extension of this of the competitively inhibit verafor signs of thismin toxicity, exate: Ibuprofen, as well as other NSAIDs, has been reported to competitively inhibit scate accumulation in rabbit kidney slices. This may indicate that ibuprofen could scate accumulation in rabbit kidney slices.

enhance the toxicity of methotrexate. Caution should be used when Combunox is administered concomitantly with methotrexate. Warfarin: The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a grader trisk of serious GI bleeding than users of either drug alone. Carcinogenicity, Mutagenicity and Impairment of Fartility Studies to evaluate the potential feets of the combination of oxycodone and ibuprofen on carcinogenicity, mutagenicity or impairment of Fartility have not been conducted.

rey Category C studies to assess the potential effects of the combination of oxycodone and ibu ryo-fetal development vere conducted in the rat and rabbit model. If rats were treated by oral gazage with combination doses of oxycodone:ibu lay (02.52.0, 0.5.40, 1.0.80, or 2.0.160) on days 7-16 of gestation. There was or developmental toxicity or teratogenicity at any does, although maternal toxic doses of 0.5.40 and above. The highest dose tested in the rat (2.00.160 mg/kg/ in to the maximum recommended human daily dose (02.1600 mg/kg/) on a bo quive... ace area (mg/i ace RW) n²) basis. This dose was as

Pregnant rabbits were treated by oral gavage with combination doses of oxycodone/ibuprofe (0.88:30, 0.75:60, 1.50:120 or 3.00:240 mol/kn/dav) on nestation down 7.40 considered b) 0.5 00 r.30 r. 20 (mortality). Th 0.75 fold the IIIIty, Title to durate the international state of the state of the proposed maximum daily human dose based upon the body surface area. opmental toxicity, as evidenced by delayed oscilication and reduced fetal body weights, olded at the highest dose, which is approximately times the MHHO on a mg/m basis, itely due to maternal toxicity. The fetal NOAEL of 1.50.120 mg/ag/day is approximately the the MHHO and a mg/m basis. are no adequate and well-controlled studies in pregnant women. Combunox should be during pregnancy only if the potential benefit justifies the potential risk to the fetus, see of the hipprofer could cause problems in the unbotn child (premature closure of the sarterious and pulmonary hypertension in the fetus/heonate).

abor and Delivery Sombunox should not be used during the third trimester of pregnancy due to the potential for build be used during the third trimester of pregnancy due to the potential for the potential of the potential of the potential of the potential for the potential of the potential of the potential of the potential for the potential of the potential the binhibit prostaglandin synthetase which may proving progradone is not recommended for use in women during and immedia ty because oral opioids may cause respiratory depression in the net provide the synthesis of the synthe

ng Mothers fore is not transferred to breast milk in significant quantities. The American A trics calssified ibuprofen as compatible with breastfeeding. In studies using a buprofen was not detected in the milk of lactating mothers. Oxycodone is o n milk. Withdrawal symptoms and/or respiratory depression have been o les whose mothers were taking narcofic analgesics during prepanacy. Althour