

Aspirin used incorrectly for cardioprotection

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ORLANDO, FLA. — Many primary care physicians do not prescribe aspirin appropriately for cardioprotection, a national survey suggests.

Many of the 1,000 primary care physicians who responded are unaware of—or disregard—data about the use of aspirin for cardioprotection and recommend to their patients doses that are too high,

William D. Chey, M.D., said at the annual meeting of the American College of Gastroenterology.

The lowest cardioprotective dose of aspirin is 81 mg/day in healthy patients and in those at risk for gastrointestinal complications. Those with gastrointestinal risk should receive gastroprotection, such as a proton pump inhibitor (PPI), Dr. Chey said.

About half of those responding to the Internet survey were internists, and half

were family physicians or general practitioners. Respondents, generally between 35 and 54 years old and evenly distributed geographically across the United States, had previously agreed to participate in survey research.

Overall, 95% said they recommend aspirin for cardioprotection in patients over age 60 years, with 62% always recommending aspirin therapy and 33% usually recommending aspirin therapy, said Dr. Chey of the University of Michigan, Ann

Arbor. Nearly 70% said they recommend 81 mg daily, but 30% said they recommend 325 mg daily. "This is relevant because there may be a dose-response relationship between aspirin and the likelihood of developing ulcer disease and, consequently, gastrointestinal bleeding," Dr. Chey said.

Another troubling finding was that 62% of respondents said they would recommend enteric-coated aspirin for a patient at high risk for gastrointestinal bleeding due to a previous ulcer bleed despite a lack of data showing any benefit of coated aspirin over regular aspirin. Also only 28% recommended concurrent gastroprotective therapy, such as with a proton pump inhibitor or misoprostol. Most said they would put the patient on aspirin alone, he said.

"I guess the good news is that [gastroenterologists] are going to stay in business if this is truly representative of primary care physicians," he said, noting that a study last year showed that the likelihood of such a high-risk patient developing recurrent gastrointestinal bleeding when put on aspirin therapy alone is about 15%.

Aspirin cardioprotection in those who require treatment with an NSAID is more controversial, Dr. Chey said. In one study of patients with a history of ulcer bleeding, the use of a PPI and NSAID and the use of a cyclooxygenase-2 (COX-2) selector alone were both associated with a recurrent bleeding rate of about 5% at 6 months.

The withdrawal of Vioxx from the market has highlighted concerns about COX-2 inhibitors and myocardial infarction risk. For now, avoiding COX-2 inhibitors in those with known coronary artery disease, Dr. Chey advised. In those without coronary artery disease who are at high risk for gastrointestinal complications, the use of a COX-2 inhibitor and PPI is warranted, but there is little or no incremental gastrointestinal safety benefit from aspirin and a COX-2 inhibitor vs. a traditional NSAID alone.

When physicians in the survey were asked about their knowledge of the effects of aspirin in patients using a COX-2 inhibitor, 69% of respondents said they were aware of the data showing that aspirin decreases or eliminates the gastrointestinal safety benefits of the COX-2 inhibitors (31% were unaware, or thought that aspirin improved the effects of COX-2 inhibitors).

Yet when asked how they would manage a patient with no history of peptic ulcer disease, but with a need for nonsteroidal antiinflammatory drug treatment for arthritis, 45% said they would recommend aspirin and a COX-2 inhibitor.

"Even more interesting, in a high-risk patient with a history of ulcer bleeding, 60% said they would recommend a proton pump inhibitor with a coxib and aspirin—even though there are no published data to support this strategy, and 24%, disturbingly, would choose a coxib and aspirin without gastroprotection," Dr. Chey said. There is no logic to this combination, he said, adding that further educational efforts are necessary to correct these "important knowledge deficits."

References: 1. Scharf MB, Roth T, Vogel GW, Walsh JK. A multicenter, placebo-controlled study evaluating zolpidem in the treatment of chronic insomnia. *J Clin Psychiatry*. 1994;55:192-199. 2. Roth T, Roehrs T, Vogel G. Zolpidem in the treatment of transient insomnia: a double-blind, randomized comparison with placebo. *Sleep*. 1995;18:246-251. 3. Eber R, Rühfer E, Furr J, Enlilien C, Salinas E, for the Zolpidem Clinical Study Group. Sleep latency is shortened during 4 weeks of treatment with zolpidem, a novel nonbenzodiazepine hypnotic. *J Clin Psychiatry*. 1999;60:536-544. 4. AMBIEN Prescribing Information. Sanofi-Synthelabo Inc. 5. Office of Applied Studies, Drug Abuse Warning Network (DAWN). Substance Abuse and Mental Health Services Administration, US Department of Health and Human Services. Reports & Issues from DAWN emergency department component. Table 1. Available at: <http://www.samhsa.gov/pubs/94/02/issue0202002.html>. Accessed December 9, 2003. 6. Hajak C, Müller WE, Wittchen HS, Pittrow D, Kirch W. Abuse and dependence potential for the non-benzodiazepine hypnotics zolpidem and zopiclone: a review of case reports and epidemiological data. *Addiction*. 2003;98:1371-1378. 7. IMS Health. National Prescription Audit Plus, MAT May 2004. 8. Data on file, Sanofi-Synthelabo Inc.

Ambien® (zolpidem tartrate)

BRIEF SUMMARY

INDICATIONS AND USAGE

Ambien (zolpidem tartrate) is indicated for the short-term treatment of insomnia. Ambien has been shown to decrease sleep latency and increase the duration of sleep for up to 35 days in a clinical trial.

Hypnotics should generally be limited to 7 to 10 days of use, and reevaluation of the patient is recommended if they are to be taken for more than 2 to 3 weeks. Ambien should not be prescribed in quantities exceeding a 30-day supply (see Warnings).

CONTRAINDICATIONS

None known.

WARNINGS

Since sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness which should be evaluated. Worsening of insomnia or the emergence of new thinking or behavior abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sedative/hypnotic drugs, including Ambien. Because some of the important adverse effects of Ambien appear to be dose related (see *Precautions and Usage Administration*), it is important to use the smallest possible effective dose, especially in the elderly.

A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedative/hypnotics. Some of these changes may be characterized by decreased inhibition (e.g., aggressiveness and extroversion that seemed out of character), similar to effects produced by alcohol and other CNS depressants. Other reported behavioral changes have included bizarre behavior, agitation, hallucinations, and depersonalization. Amnesia and other neuropsychiatric symptoms have also occurred. In normally sober and sober patients, worsening of depression, including suicidal thinking, has been reported in association with the use of sedative/hypnotics.

It can rarely be determined whether a particular instance of the abnormal behaviors listed above is drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral signs or symptoms of concern requires careful and immediate evaluation.

Following the rapid dose decrease or abrupt discontinuation of sedative/hypnotics, there have been reports of symptoms similar to those associated with withdrawal from other CNS-depressant drugs (see *Drug Abuse and Dependence*).

Ambien, like other sedative/hypnotic drugs, has CNS-depressant effects. Due to the rapid onset of action, Ambien should only be ingested immediately prior to going to bed. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination, such as operating machinery or driving a motor vehicle after ingesting the drug, including potential impairment of the performance of such activities that may occur the day following ingestion. Ambien should be used with caution when combined with alcohol and should not be taken with alcohol. Patients should also be cautioned about possible combined effects with other CNS-depressant drugs. Dosage adjustments may be necessary when Ambien is administered with such agents because of the potentially additive effects.

PRECAUTIONS

General
Use in elderly and/or debilitated patients: Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative/hypnotic agents is a concern in the treatment of elderly and/or debilitated patients. Therefore, the recommended Ambien dosage in such patients (see *Dosage and Administration*) to decrease the possibility of side effects. These patients should be closely monitored.

Use in patients with concomitant illness: Clinical experience with Ambien in patients with concomitant chronic medical illness is limited. Caution is advisable in using Ambien in patients with diseases or conditions that could affect metabolism or hemodynamic responses. Although studies did not reveal respiratory depressant effects at hypnotic doses, Ambien in normal or in patients with mild to moderate chronic obstructive pulmonary disease (COPD), a reduction in the Total Arterial Index together with a reduction in lowest oxygen saturation and increase in the time to desaturate below 90%, and 30% was observed in patients with mild-to-moderate sleep apnea when treated with Ambien (10 mg) when compared to placebo. However, precautions should be observed if Ambien is prescribed in combination with a pharmacologic agent, since sedative/hypnotics have the capacity to depress respiratory drive. Post-marketing reports of respiratory insufficiency, most of which involved patients with preexisting respiratory impairment, have been received. Data in end-stage renal failure patients repeatedly treated with Ambien did not demonstrate drug accumulation or alterations in pharmacokinetic parameters. No dosage adjustment in renal impairment is required; however, these patients should be closely monitored (see *Pharmacokinetics*). A study in subjects with hepatic impairment revealed prolonged elimination in this group; therefore, treatment should be initiated with 5 mg in patients with hepatic compromise, and they should be closely monitored.

Use in depression: As with other sedative/hypnotic drugs, Ambien should be administered with caution to patients exhibiting signs or symptoms of depression. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional overdose is more common in this group of patients; therefore, the least amount of drug that is feasible should be prescribed for the patient at any one time.

Information for patients: Patient information is printed in the complete prescribing information.

Laboratory tests: There are no specific laboratory tests recommended.

Drug interactions
CNS-active drugs: Ambien was evaluated in healthy volunteers in single-dose interaction studies for several CNS drugs. A study involving haloperidol and zolpidem revealed no effect of haloperidol on the pharmacokinetics or pharmacodynamics of zolpidem. In another study, zolpidem did not affect the pharmacokinetic interaction other than a 20% decrease in peak levels of imipramine, but there was an additive effect of decreased alertness. Similarly, chlorpromazine in combination with zolpidem produced no pharmacologic interaction, but there was an additive effect of decreased alertness and psychomotor performance. The lack of a drug interaction following single-dose administration does not predict a lack following chronic administration.

An additive effect on psychomotor performance between alcohol and zolpidem was demonstrated. A single-dose interaction study with zolpidem 10 mg and fluoxetine 20 mg at steady-state levels in male volunteers did not demonstrate any clinically significant pharmacokinetic or pharmacodynamic interactions. When multiple doses of zolpidem and fluoxetine at steady-state concentrations were evaluated in healthy females, the only significant change was a 17% increase in the zolpidem half-life. There was no evidence of an additive effect in psychomotor performance. Following five consecutive nights of zolpidem 10 mg in the presence of sertraline 50 mg (17 consecutive daily doses, at 7:00 am, in healthy female volunteers), zolpidem C_{max} was significantly higher (43%) and $T_{1/2}$ was significantly decreased (53%). Pharmacokinetics of sertraline and N -desmethylsertraline were unaffected by zolpidem.

Since the systematic evaluation of Ambien in combination with other CNS-active drugs has been limited, caution should be exercised in giving to the pharmacology of any CNS-active drug to be used with zolpidem. Any drug with CNS-depressant effects could potentially enhance the CNS-depressant effects of zolpidem.

Drugs that affect drug metabolism via cytochrome P450: A randomized, double-blind, crossover interaction study in healthy volunteers between itraconazole (200 mg once daily for 4 days) and a single dose of zolpidem (10 mg) given 5 hours after the last dose of itraconazole resulted in a 24% increase in AUC of zolpidem. There were no significant pharmacodynamic effects of zolpidem on subjective drowsiness, postural sway, or psychomotor performance.

A randomized, placebo-controlled, crossover interaction study in eight healthy female volunteers between 5 consecutive daily doses of rifampin (600 mg) and a single dose of zolpidem (10 mg) given 17 hours after the last dose of rifampin resulted in significant reductions of AUC of zolpidem (15%) and C_{max} (18%) of zolpidem together with significant reductions in the pharmacodynamic effects of zolpidem.

Other drugs: A study involving cimetidine/zolpidem and ranitidine/zolpidem combinations revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of zolpidem. Zolpidem had no effect on digoxin kinetics and did not affect prothrombin time when given with warfarin in normal subjects. Zolpidem's sedative/hypnotic effect was reversed by flumazenil; however, no significant alterations in zolpidem pharmacokinetics were found.

Drug-laboratory test interactions: Zolpidem is not known to interfere with commonly employed clinical laboratory tests. In addition, clinical data indicate that zolpidem does not cross-react with benzodiazepines, opiates, barbiturates, cocaine, cannabinoids, or amphetamines in two standard urine drug screens.

Carcinogenesis, mutagenesis, impairment of fertility
Animals: Zolpidem was administered to male and female rats for 2 years at dietary dosages of 4, 18, and 80 mg/kg/day. In mice, these doses were 2 to 250 times or 2 to 35 times the maximum 10-mg human dose on a mg/kg or mg/m² basis, respectively. In rats, these doses were 45 to 978 times or 8 to 115 times the maximum 10-mg human dose on a mg/kg or mg/m² basis, respectively. No evidence of carcinogenic potential was observed in mice. Rats liposarcomas were seen in 100 rats (3 males and 7 females) treated with 80 mg/kg/day and a renal lipoma was observed in one male rat at the 18 mg/kg/day dose. Incidence rates of lipoma and liposarcoma for zolpidem were comparable to those seen in historical controls and the tumor findings are thought to be a spontaneous occurrence.

Mutagenesis: Zolpidem did not have mutagenic activity in several tests including the Ames test, genotoxicity in mouse lymphoma cells in vitro, chromosomal aberrations in cultured human lymphocytes, unscheduled DNA synthesis in rat hepatocytes in vivo, and the micronucleus test in normal subjects.

Impairment of fertility: In a rat reproduction study, the high dose (100 mg/kg) of zolpidem resulted in irregular estrus cycles and prolonged preovulatory intervals, but there was no effect on male or female fertility after oral doses of 100 mg/kg based on a 7 to 150 times the recommended human dose of mg/m². No effects on any other fertility parameters were noted.

Pregnancy
Teratogenic effects: Category B. Studies to assess the effects of zolpidem on reproduction and development have not been conducted.

Toxicology studies: Studies were conducted in rats and rabbits. In rats, adverse maternal and fetal effects occurred at 20 and 100 mg/kg and included decreased maternal body weight and a dose-related trend to incomplete ossification of fetal skull bones. In rabbits, dose-related maternal and/or decreased weight gain occurred at all doses tested. At the high dose, 16 mg/kg, there was an increase in postimplantation fetal loss and underossification of sternebrae in viable fetuses.

This drug should be used during pregnancy only if clearly needed.

Nonteratogenic effects: Studies to assess the effects on children whose mothers took zolpidem during pregnancy have not been conducted. However, children born to mothers taking sedative/hypnotic drugs may display some risk for withdrawal symptoms from the drug during the postnatal period. In addition, neonatal fatality has been reported in infants born to mothers who received sedative/hypnotic drugs during pregnancy.

Labor and delivery: Ambien has no established use in labor and delivery.

Nursing mothers: Studies in lactating mothers indicate that between 0.004 and 0.019% of the total administered dose is excreted into milk, but the effect of zolpidem on the infant is unknown.

The use of Ambien in nursing mothers is not recommended.

Pediatric use: Safety and effectiveness in pediatric patients below the age of 18 have not been established.

Geriatric use: A total of 154 patients in U.S. controlled clinical trials and 897 patients in non-U.S. clinical trials received zolpidem between 20 and 89 years of age. For a pool of U.S. patients receiving zolpidem at doses of 5 mg or placebo, there were three adverse events occurring at an incidence of at least 3% for zolpidem and for which the zolpidem incidence was at least twice the placebo incidence (i.e., they were considered drug related): drowsiness (10%), dizziness (6%), and falls (4%).

Approximately 4% of 1959 patients who received zolpidem at all doses (1 to 50 mg) in similar form factor trials discontinued treatment because of an adverse event. Events most commonly associated with discontinuation from these trials were drowsiness (2%), dizziness (2%), headache (2%), nausea (0.5%), and falls (0.5%).

Data from a clinical study in which selective serotonin reuptake inhibitor (SSRI) treated patients were given zolpidem at doses up to 10 mg and placebo during long-term treatment (28 to 35 nights) with zolpidem at doses up to 10 mg, the most commonly observed adverse events associated with the use of zolpidem seen at statistically significant differences from placebo-treated patients were drowsiness (2%) and falls (0.5%).

Treatment-emergent adverse experiences in placebo-controlled clinical trials: The following are treatment-emergent adverse events from U.S. placebo-controlled clinical trials. Data are limited to data from doses up to 10 mg. In short-term trials, events seen in zolpidem patients (n=685) at an incidence equal to 1% or greater compared to placebo (n=473) were: headache (7% vs 6% for placebo), drowsiness (2% vs 2%), dizziness (1% vs 1%), nausea (0.2% vs 0.2%), diarrhea (1% vs 0%), and myalgia (1% vs 2%). In long-term clinical trials, events seen in zolpidem patients (n=152) at an incidence of 1% or greater compared to placebo (n=161) were: dry mouth (3% vs 1% for placebo), allergy (4% vs 1%),

back pain (3% vs 2%), influenza-like symptoms (2% vs 0%), chest pain (1% vs 0%), fatigue (1% vs 2%), palpitation (2% vs 0%), headache (19% vs 22%), drowsiness (5% vs 5%), dizziness (5% vs 1%), lethargy (3% vs 1%), drugged feeling (3% vs 0%), lightheadedness (2% vs 1%), depression (2% vs 1%), abnormal vision (1% vs 0%), amnesia (1% vs 0%), anxiety (1% vs 1%), nervousness (1% vs 3%), sleep disorder (1% vs 0%), nausea (0% vs 0%), dyspepsia (0% vs 0%), diarrhea (0% vs 0%), abdominal pain (2% vs 2%), constipation (2% vs 1%), anorexia (1% vs 1%), vomiting (1% vs 1%), infection (1% vs 1%), myalgia (7% vs 7%), arthralgia (4% vs 4%), upper respiratory infection (5% vs 6%), sinusitis (4% vs 2%), pharyngitis (3% vs 1%), rhinitis (1% vs 3%), rash (2% vs 1%), and urinary tract infection (2% vs 2%).

Dose relationship for adverse events: There is evidence from dose comparison data suggesting that the incidence of adverse events increases with increasing dose with zolpidem use, particularly for certain CNS and gastrointestinal adverse events.

Adverse events are further classified and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in greater than 1100 subjects; infrequent adverse events are those occurring in 1100 to 1/1000 subjects; rare events are those occurring in less than 1/1000 patients.

Frequent: abdominal pain, abnormal dreams, allergy, amnesia, anorexia, anxiety, arthralgia, asthenia, ataxia, back pain, chest pain, confusion, constipation, depression, diarrhea, diplopia, dizziness, drowsiness, drugged feeling, dry mouth, dyspepsia, euphoria, fatigue, headache, hiccups, infection, influenza-like symptoms, insomnia, lethargy, lightheadedness, myalgia, nausea, nervousness, palpitation, sleep disorder, vertigo, vision abnormal, vomiting.

Infrequent: abnormal hepatic function, agitation, arthritis, brachitis, cerebrovascular disorder, coughing, cystitis, decreased cognition, decreased, difficulty concentrating, dysarthria, dysphasia, dyspnea, emotional lability, eye irritation, eye pain, falling fever, fatigue, gastroenteritis, hallucination, hyperglycemia, hypertension, hypohydrosis, insulin, increased SGPT, increased sweating, leg cramps, male, menstrual disorder, migraine, pallor, paraesthesia, postural hypotension, pruritus, scabies, sleeping after daytime dosing, speech disorder, stupor, syncope, tachycardia, taste perversion, tinnitus, tremor, trauma, tremor, urinary incontinence, vaginitis.

Rare: abnormal body sensation, abnormal accommodation, abnormal gait, abnormal thinking, abnormal vision, acute renal failure, aggressive reaction, allergic reaction, allergy aggravated, altered saliva, anaphylactic shock, anemia, angina pectoris, anorexia, appetite increased, arrhythmia, arthritis, arthralgia, bilirubinemia, breast fibroadenoma, breast pain, breast fibrocystosis, bulimic eruption, circulatory failure, conjunctivitis, corneal ulceration, decreased libido, delusion, dementia, depersonalization, dermatitis, dysphasia, dysuria, edema, epistaxis, erection, esophagospasm, extravasation, facial edema, flushing, flushing, furunculosis, gastritis, glaucoma, gout, hemorrhoids, herpes simplex, herpes zoster, host, hives, hypercholesterolemia, hyperhemoglobinemia, hypotension, hypokalemia, hypotension, hypotension, hypotension, hypotension, hypoxia, hysteria, impotence, increased alkaline phosphatase, increased BUN, increased ESR, increased salivary, increased SGPT, injection-site irritation, intestinal obstruction, increased salivary, lacrimation abnormal, laryngitis, leukopenia, lymphadenopathy, macrocytic anemia, manic reaction, myocardial infarction, muscle weakness, myocardial infarction, neuralgia, neuritis, neurophy, neuritis, nocturia, otitis externa, otitis media, pain, panic attacks, paresis, paronychia, periorbital edema, personality disorder, phlebitis, photopsia, photosensitivity reaction, pneumonia, polyuria, pulmonary edema, pulmonary embolism, purpura, pyelonephritis, renal hemorrhage, renal pain, restless legs, rigors, scotoma, somnambulism, suicide attempts, tendinitis, tetanus, tetany, thrombosis, tolerance increased, tooth caries, urinary retention, urticaria, varicose veins, ventricular tachycardia, weight decrease, yawning.

DRUG ABUSE AND DEPENDENCE

Controlled substance:

Abuse and dependence: Studies of abuse potential in former drug abusers found that the effects of single doses of zolpidem tartrate 40 mg were similar, but not identical, to diazepam 20 mg, while zolpidem tartrate 10 mg was difficult to distinguish from placebo.

Sedative/hypnotics have produced withdrawal signs and symptoms following abrupt discontinuation. These reported symptoms range from mild dysphoria and insomnia to a withdrawal syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors, and convulsions. The U.S. clinical trial experience from zolpidem does not reveal any clear evidence for withdrawal syndrome. Nevertheless, the following adverse events included in DSM-IV criteria for unrecognized sedative/hypnotic withdrawal syndrome occurred at an incidence of 1% during U.S. clinical trials following placebo substitution occurring within 48 hours following last zolpidem treatment: fatigue, nausea, flushing, lightheadedness, uncontrollable cry, muscle cramps, panic attack, pain, nervousness, and abdominal discomfort. Rare post-marketing reports of abuse, dependence and withdrawal have been received.

Individuals with a history of abuse of drugs or alcohol are at increased risk of habituation and dependence; they should be under careful surveillance when receiving any hypnotic.

OVERDOSEAGE

Signs and symptoms: In European post-marketing reports of overdose with zolpidem alone, impairment of consciousness has ranged from somnolence to light coma, with one case each of cardiovascular and respiratory compromise. Individuals have fully recovered from zolpidem tartrate overdoses up to 400 mg (40 times the maximum recommended dose). Overdose cases involving multiple CNS-depressant agents, including zolpidem, have resulted in more severe symptomatology, including fatal outcomes.

Recommended treatment: General symptomatic and supportive measures should be used along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Flumazenil may be useful for respiratory depression, but blood pressure, and other appropriate signs should be monitored and general supportive measures employed. Sedating drugs should be withheld following zolpidem overdose. Zolpidem is not dialyzable.

The possibility of multiple drug ingestion should be considered.

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