

Keep Priorities Straight When Treating Eclampsia

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Contributing Writer

NEW YORK — Eclampsia has become increasingly rare in Western countries, but it still occurs in 1 in 2,000-3,500 pregnancies—and obstetric clinics must be prepared to treat it, Baha M. Sibai, M.D., said at an obstetrics symposium sponsored by Columbia University and New York Presbyterian Hospital.

Although most episodes occur late in

pregnancy, an increasing number occur more than 2 days after delivery, and patients should be counseled accordingly, said Dr. Sibai, professor and chairman of the obstetrics and gynecology department at the University of Cincinnati.

Eclampsia does not always come with a warning. It has been reported that in 15%-20% of cases neither hypertension nor proteinuria has occurred.

“Most women with eclampsia have had good prenatal care,” Dr. Sibai said. In a

1992 U.K. study of 383 women, 85% had been seen by a medical care provider within a week before the episode.

Eclampsia is largely a late event: in a sample of 399 U.S. women, the episode occurred after the 32nd week of gestation in 72%, and before week 28 in roughly 10%.

In a substantial number of cases—28%, in the U.S. study—the condition developed after delivery; in two-thirds of these cases, it happened more than 48 hours later.

“More and more, the onset of convulsions is in the postpartum period. We’ve done an excellent job educating women to report signs and symptoms during pregnancy, but a poor one in educating them that they can have eclampsia after leaving the hospital,” Dr. Sibai said.

The lapse can have medicolegal implications, he said.

Emergency management of eclampsia should focus on protecting the mother from injury (e.g., cushioning extremities and preventing a fall off the bed), ensuring adequate oxygenation, and preventing aspiration. Once these are addressed, steps should be taken to avoid recurrent convulsions.

“Never give anything to stop the convulsion: no one dies from a seizure, and you

could do damage if you give the wrong dose,” Dr. Sibai said. Most seizures are self-limiting, and medications to contain them may depress respiration. Hypertension should be the next concern, and then delivery. “[It] should be the last thing on your mind,” he said.

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If hypoxemia develops, 8-10 L/min of supplementary oxygen should be supplied by face mask, and pulse oximetry monitored. Sodium bicarbonate may be required for acidemia.

To prevent further convulsions, IV magnesium sulfate should be begun with a loading dose of 6 g over a 20-minute period, followed by maintenance at 2 g/hour. The anticonvulsants diazepam and phenytoin, which can depress respiration and compromise alveolar reflexes, carry a higher mortality rate and should be avoided.

“Don’t listen to what the neurologist or internist tells you to do,” Dr. Sibai said.

The risk of magnesium toxicity should be kept in mind: look for such signs of rising serum levels as double vision, a feeling of warmth or flushing, and lethargy; monitor patellar reflexes hourly.

“Always talk to the patient. Slurred speech shows paralysis of the muscles of the jaw,” he said.

Magnesium sulfate should be discontinued immediately while a blood level is taken, and restarted with appropriate adjustments. If serum magnesium is above 15 mg/dL—a level that threatens respiratory and cardiac arrest—1 g of calcium gluconate should be given intravenously and intubation and assisted ventilation provided if necessary.

For control of severe hypertension, labetalol and nifedipine are drugs of choice; hydralazine should be avoided, he said.

When possible, delivery should be done within 24 hours. Cesarean delivery is not always necessary, and vaginal delivery can be done with epidural or spinal anesthesia.

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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 controlled clinical studies.

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 1-month 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 Dosage and 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 (ie, 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 may occur unpredictably. In primarily depressed patients, worsening of depression, including suicidal thinking, has been reported in association with the use of sedative/hypnotics.

It can rarely be determined with certainty 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 sign or symptom of concern requires careful and immediate evaluation.

Following the rapid dose decrease or abrupt discontinuation of sedative/hypnotics, there have been reports of signs and 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 of Ambien. 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 the elderly and/or debilitated patients: Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative/hypnotic drugs is a concern in the elderly and/or debilitated patients. Therefore, the recommended Ambien dosage is 5 mg 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 systemic 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 of Ambien in normals or in patients with mild to moderate chronic obstructive pulmonary disease (COPD), a reduction in the Total Arousal Index together with a reduction in lowest oxygen saturation and increase in the times of oxygen desaturation below 80% and 90% 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 to patients with compromised respiratory function, since sedative/hypnotics have the capacity to depress respiratory drive. Post-marketing reports of respiratory insufficiency, most of which involved patients with pre-existing 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 is usually required; however, these patients should be closely monitored (see *Pharmacokinetics*). A study in subjects with hepatic impairment did reveal 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. Imipramine in combination with zolpidem produced no 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 pharmacokinetic 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 nightly doses 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 evaluations of Ambien in combination with other CNS-active drugs have been limited, careful consideration should be given 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 ten 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 34% increase in AUC_{0-12} 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 (20 mg) given 17 hours after the last dose of rifampin showed significant reductions of the AUC (-73%), C_{max} (-58%), and $T_{1/2}$ (-36%) 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

Carcinogenesis: Zolpidem was administered to rats and mice for 2 years at dietary doses of 4, 18, and 80 mg/kg/day. In mice, these doses are 26 to 520 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 are 43 to 876 times or 6 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. Renal liposarcomas were seen in 4/100 rats (3 males, 1 female) receiving 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, mutagenicity in mouse lymphoma cells in vitro, chromosomal aberrations in cultured human lymphocytes, unscheduled DNA synthesis in rat hepatocytes in vitro, and the micronucleus test in mice.

Impairment of fertility: In a rat reproduction study, the high dose (100 mg base/kg) of zolpidem resulted in irregular estrus cycles and prolonged preovulatory intervals, but there was no effect on male or female fertility after daily oral doses of 4 to 100 mg base/kg or 5 to 130 times the recommended human dose in mg/m². No effects on any other fertility parameters were noted.

Pregnancy

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

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

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

Neonatal effects: Studies to assess the effects on children whose mothers took zolpidem during pregnancy have not been conducted. However, children born of mothers taking sedative/hypnotic drugs may be at some risk for withdrawal symptoms from the drug during the postnatal period. In addition, neonatal flaccidity has been reported in infants born of 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 who received zolpidem were ≥60 years of age. For a pool of U.S. patients receiving zolpidem at doses of ≤10 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 (ie, they could be considered drug related).

Adverse Event	Zolpidem	Placebo
Dizziness	3%	0%
Drowsiness	5%	2%
Diarrhea	3%	1%

A total of 301,959 (1.5%) non-U.S. patients receiving zolpidem reported falls, including 29,300 (9.5%) who were ≥70 years of age. Of these 29 patients, 23 (82%) were receiving zolpidem doses >10 mg. A total of 241,959 (1.2%) non-U.S. patients receiving zolpidem reported confusion, including 18,244 (7.5%) who were ≥70 years of age. Of these 18 patients, 14 (78%) were receiving zolpidem doses >10 mg.

ADVERSE REACTIONS

Associated with discontinuation of treatment: Approximately 4% of 1,701 patients who received zolpidem at all doses (1.25 to 90 mg) in U.S. premarketing clinical trials discontinued treatment because of an adverse clinical event. Events most commonly associated with discontinuation from U.S. trials were daytime drowsiness (0.5%), dizziness (0.4%), headache (0.5%), nausea (0.8%), and vomiting (0.5%).

Approximately 4% of 1,959 patients who received zolpidem at all doses (1 to 50 mg) in similar foreign trials discontinued treatment because of an adverse event. Events most commonly associated with discontinuation from these trials were daytime drowsiness (1.1%), dizziness/vertigo (0.8%), amnesia (0.5%), nausea (0.5%), headache (0.4%), and falls (0.4%).

Data from a clinical study in which selective serotonin reuptake inhibitor (SSRI) treated patients were given zolpidem revealed that four of the seven discontinuations during double-blind treatment with zolpidem (n=95) were associated with impaired concentration, continuing or aggravated depression, and manic reaction; one patient treated with placebo (n=97) was discontinued after an attempted suicide.

Incidence in controlled clinical trials

Most commonly observed adverse events in controlled trials: During short-term treatment (up to 10 nights) with Ambien at doses up to 10 mg, the most commonly observed adverse events associated with the use of zolpidem and seen at statistically significant differences from placebo-treated patients were drowsiness (reported by 2% of zolpidem patients), dizziness (1%), and diarrhea (1%). During longer-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 and seen at statistically significant differences from placebo-treated patients were dizziness (5%) and drugged feelings (3%).

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 and including 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 0%), dizziness (1% vs 0%), nausea (2% vs 3%), 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 (8% vs 5%), dizziness (5% vs 1%), lethargy (3% vs 1%), drugged feeling (3% vs 0%), lightheadedness (2% vs 1%), depression (2% vs 1%), abnormal dreams (1% vs 0%), amnesia (1% vs 0%), anxiety (1% vs 1%), nervousness (1% vs 3%), sleep disorder (1% vs 0%), nausea (6% vs 6%), dyspepsia (5% vs 6%), diarrhea (3% vs 2%), 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 trials suggesting a dose relationship for many of the adverse events associated 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 1/100 subjects; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 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, hiccup, infection, influenza-like symptoms, insomnia, lethargy, lightheadedness, myalgia, nausea, nervousness, palpitation, sleep disorder, vertigo, vision abnormal, vomiting.

Infrequent: abnormal hepatic function, agitation, arthritis, bronchitis, cerebrovascular disorder, coughing, cystitis, decreased cognition, detached, difficulty concentrating, dysarthria, dysphagia, dyspnea, edema, emotional lability, eye irritation, eye pain, falling, fever, flatulence, gastroenteritis, hallucination, hyperglycemia, hypertension, hypoesthesia, illusion, increased SGPT, increased sweating, leg cramps, malaise, menstrual disorder, migraine, pallor, paresthesia, postural hypotension, pruritus, scalditis, sleeping (after daytime dosing), speech disorder, stupor, syncope, tachycardia, taste perversion, tinnitus, trauma, tremor, urinary incontinence, vaginitis.

Rare: abdominal body sensation, abnormal accommodation, abnormal gait, abnormal thinking, abscess, acne, acute renal failure, aggressive reaction, allergic reaction, allergy aggravated, altered saliv, anaphylactic shock, anemia, angina pectoris, apathy, appetite increased, arrhythmia, arteritis, arthrosis, bilirubinemia, breast fibroadenosis, breast neoplasm, breast pain, bronchospasm, bullous eruption, circulatory failure, conjunctivitis, corneal ulceration, decreased libido, delusion, dementia, depersonalization, dermatitis, dysphasia, dysuria, enteritis, epistaxis, eruption, esophagospasm, extrastyles, face edema, feeling, numbness, neurosis, nocturia, otitis externa, otitis media, pain, panic attacks, parosmia, parosmia, periorbital edema, personality disorder, phlebitis, photopsia, photosensitivity reaction, pneumonia, polyuria, pulmonary edema, pulmonary embolism, purpura, pyelonephritis, rectal hemorrhage, renal pain, restless legs, rickets, sciatia, 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: Schedule IV.

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-III-R criteria for uncomplicated sedative/hypnotic withdrawal were reported 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, uncontrolled crying, emesis, stomach cramps, panic attack, nervousness, and abdominal discomfort. Rare post-marketing reports of abuse, dependence and withdrawal have been received.

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

OVERDOSAGE

Signs and symptoms: In European postmarketing 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. Respiration, pulse, 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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