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**Haloperidol and cardiovascular concerns**

On September 17, 2007, a warning about cardiovascular risks associated with haloperidol was announced by Johnson and Johnson and the U.S. Food and Drug Administration (FDA). Several case reports of patients receiving intravenous haloperidol at higher than recommended doses have documented QT prolongation, Torsades de Pointes (TdP), and even sudden death.

**Haloperidol use**

Haloperidol lactate injection, approved for intramuscular administration, is indicated for use in schizophrenia and for the control of tics and vocal utterances associated with Tourette's Disorder. Haloperidol is commonly administered off-label as an intravenous (IV) injection for delirium, although it is not FDA-approved for this route of administration or indication.

Delirium may occur in 10% to 30% of hospitalized patients, and symptoms may last more than 2 months. Antipsychotics are generally considered the drugs of choice for delirium, and haloperidol is considered first-line due to its relatively tolerable adverse effect profile and extensive clinical experience with its use. The Society of Critical Care Medicine and the American College of Critical Care Medicine consider haloperidol the drug of choice for the treatment of delirium in critically ill patients. IV administration is considered most effective for achieving sedation in emergency situations or when oral access is limited.

Cardiovascular concerns with haloperidol tend to be associated with IV administration and higher doses. The optimal dose for delirium has not been established, and a large range of doses have been used. Doses as low as 0.25 mg every 4 hours may be sufficient for geriatric patients with delirium; however, there are reports of adult patients who have required single intravenous doses up to 50 mg or total daily dosages of 500 mg.

**Reports of cardiovascular risks**

The mechanism by which haloperidol affects the cardiac conduction system is unclear; however, it has been shown to block the cardiac sodium and aortic calcium channels in animal studies. Numerous case reports have demonstrated QT prolongation, TdP, and fatality associated with haloperidol use. Seventy-three cases of TdP, 11 of which were fatal, were reported in a post-marketing analysis of adverse events related to oral or injectable haloperidol. The sponsor reported concomitant use of QT-prolonging drugs or medical conditions in many of these cases. Another post-marketing investigation examined cardiac adverse events with haloperidol decanoate, the long-acting intramuscular formulation. Thirteen cases of TdP, QT prolongation, ventricular arrhythmias and/or sudden death were reported.

Case-control studies have demonstrated a dose-dependent relationship between intravenous haloperidol and subsequent TdP. Along with increased risks of other adverse effects with higher dosages, some evidence suggests that the risk of TdP increases at total daily dosages of 35 to 50 mg or more. Limited evidence suggests the incidence of TdP in patients receiving haloperidol intravenously is about 0.4% to 3.6%, but it may increase to greater than 10% at intravenous doses of 35 mg or more per day.

**Recommendations**

Due to cardiovascular risks associated with the use of IV haloperidol and other antipsychotic agents, recommendations to prevent adverse events include:

- Recognizing predisposing factors, such as underlying cardiac abnormalities, hypothyroidism, or familial long QT syndrome
- Performing baseline and periodic electrocardiograms (ECGs) with special

- attention paid to the length of the QTc interval
- Ordering telemetry, a cardiology consultation, and dose reduction or discontinuation of haloperidol if the QTc interval is prolonged to greater than 450 msec or to greater than 15% to 25% over that in previous ECGs
- Monitoring serum concentrations of magnesium and potassium in critically ill patients
- Avoiding concomitant use with other QT prolonging drugs
  - Antiarrhythmics
    - Class IA (quinidine, procainamide, disopyramide)
    - Class III (dofetilide, ibutilide, sotalol, amiodarone)
  - Antimicrobials
    - Macrolides (erythromycin, clarithromycin)
    - Antiprotozoals (pentamidine)
    - Antimalarials (halofantrine, chloroquine)
  - Antipsychotics
    - Phenothiazines (thioridazine, chlorpromazine, mesoridazine)
    - Butyrophenones (droperidol)
    - Diphenylpiperidines (pimozide)
  - Miscellaneous medications
    - Arsenic trioxide
    - Methadone
  - Vitamins, supplements, herbal medications (licorice)
  - Visit [www.torsades.org](http://www.torsades.org) for more information regarding medications that may increase the risk of QT prolongation

## Conclusion

Haloperidol is the drug of choice for delirium, and it has been widely used intravenously off-label for this use; case reports indicate the risk of TdP, QT prolongation, and possible sudden death. The likelihood of these events is typically associated with higher than recommended intravenous doses. However, they have also been reported at lower doses. Baseline and periodic ECGs should be performed in patients receiving haloperidol, and special precautions should be taken in patients at higher risk for developing QT prolongation.

## Recent Warnings Regarding Sedative-Hypnotic Medications

Insomnia defined, as difficulty initiating or maintaining sleep, waking up too early or poor-quality sleep, is the most common sleep disorder in adults. In fact, one third of adults experience occasional insomnia and 1 in 10 has chronic insomnia (at least 3 nights per week for more than a month). It is more likely to occur in women than men and older versus younger adults; other risk factors include high

stress levels, depression, variable work hours and travel with time changes. Most cases are comorbid with other conditions that may disrupt sleep, particularly depression and substance use, cardiopulmonary disorders, and conditions associated with somatic complaints such as pain and gastrointestinal disorders. Chronic insomnia is a serious problem that can impact mood, safety, cognitive function, work performance and quality of life. Insomnia affects not only individual patients but also families, caregivers, and friends. It is associated with high health care utilization; annual direct and indirect costs of chronic insomnia are estimated to be tens of billions of dollars. Available treatments for insomnia include a variety of cognitive and behavioral therapies; antidepressant, antipsychotic or antihistamine medications; and sedative-hypnotic medications.

Many people turn to prescription sedative-hypnotic medications for relief of insomnia. The benzodiazepine receptor agonists consist of benzodiazepines (estazolam, flurazepam, quazepam, temazepam, and triazolam) and non-benzodiazepines (zaleplon, zolpidem, and eszopiclone). The newest agent for the treatment of insomnia is ramelteon, a melatonin receptor agonist. Adverse effects associated with sedative-hypnotics include residual daytime sedation, cognitive impairment, motor incoordination, dependence and rebound insomnia; however, the frequency and severity are much lower for the non-benzodiazepines.

“Ambien drivers” have made news headlines as blood levels of the drug have been found in drivers arrested for erratic behavior or suspected intoxication, and researchers have reported instances of complex sleep-related behaviors. The published literature contains a number of case reports associated with sedative-hypnotic use including sleepwalking, nocturnal eating and sleep related eating disorder, compulsive repetitive behaviors such as cleaning and shopping, and other complex behaviors such as attempting to fill a lawn mower with gasoline, often with amnesia for the events. Cases of amnesia with robbery, sexual assault, automatism and attempted murder have also been reported in patients taking benzodiazepines.

Researchers’ data and adverse events reported to MedWatch prompted the FDA to examine the sedative-hypnotic drugs’ potential for causing sleep driving. Over a dozen complex sleep-related behaviors associated with the medications, such as driving, eating, cooking, and having sex while asleep, were reported. The behaviors can be triggered by concomitant alcohol or other drugs affecting the central nervous system. The FDA also examined the potential for allergic reactions after receiving reports of angioedema in patients taking ramelteon. Reports of anaphylaxis and sleep behaviors were rare, and no deaths have been reported as a direct result of taking the drugs.

In March 2007, the FDA issued new warnings for sedative-hypnotics and requested the following of manufacturers: (1) label change to include stronger language regarding potential risks, including complex sleep-related behaviors, such as sleep-driving, and severe allergic reactions (anaphylaxis and angioedema) which can occur as early as the first use; (2) letters to healthcare providers regarding revised labeling; and (3) Patient Medication Guides for distribution by pharmacists to patients receiving sedative-hypnotics to provide information on risks and precautions to be taken, proper use and avoidance of alcohol and/or other central nervous system depressants. The FDA also recommended that manufacturers conduct clinical studies to investigate the frequency of complex sleep-related behaviors associated with individual products.

The revised labeling and Patient Medication Guides warn against complex sleep-related behaviors. The zolpidem and eszopiclone package inserts (PIs) state "There have been reports of people getting out of bed after taking a sedative-hypnotic and driving their cars while not fully awake, often with no memory of the event. If a patient experiences such an episode, it should be reported to his or her doctor immediately, since "sleep-driving" can be dangerous. This behavior is more likely to occur when Ambien CR [or Lunesta] is taken with alcohol or other central nervous system depressants. Other complex behaviors (e.g., preparing and eating food, making phone calls, or having sex) have been reported in patients who are not fully awake after taking a sedative-hypnotic. As with "sleep-driving", patients usually do not remember these events." The zaleplon PI adds that the events can occur in sedative-hypnotic-naïve or -experienced persons.

Patients should be instructed to report all concomitant medications to their prescriber, as well as events such as "sleep-driving" and other complex behaviors immediately. Neuropsychiatric symptoms and amnesia are unpredictable. Because of the risk to both the patient and the community, discontinuation of the medication should be strongly considered in patients who experience a "sleep-driving" episode.

Medications affected by the warnings include: Ambien/ Ambien CR (zolpidem), Lunesta (eszopiclone), Sonata (zaleplon), Rozerem (ramelteon), Butisol Sodium (butabarbital), Dalmane (flurazepam hydrochloride), Doral (quazepam), Halcion (triazolam), Prosom (estazolam), Restoril (temazepam) and Seconal (secobarbital sodium).

### **EDTA Medication Errors**

The FDA has alerted providers to medication errors involving the confusion of 2 similar sounding drug products, edetate disodium and edetate calcium disodium. Edetate disodium, labeled to treat hypercalcemia in emergency situations and arrhythmias due to digoxin toxicity, is rarely used in current clinical practice due to availability of alternative therapies that are not nephrotoxic. On the other hand, edetate calcium

disodium, a chelating agent, is commonly used for severe lead poisoning.

Medication errors occur when edetate disodium is given instead of edetate calcium disodium to pediatric patients. The error leads to severe hypocalcemia and has been fatal in at least 2 cases. In addition, an adult expired after receiving edetate disodium administered by a naturopathic practitioner; this death was also due to hypocalcemia.

The FDA suggests hospitals consider eliminating edetate disodium from the formulary in order to prevent this type of look-alike, sound-alike medication error. If edetate disodium is needed in the institution, FDA suggests the use of the full product name (instead of EDTA) and that the indication should be specified on the prescription too. Pharmacists, nurses, and other healthcare providers should carefully review orders for these products and be especially vigilant.

### **UIMCC New Policy for Pharmaceutical Representatives**

Effective Monday, March 17, 2008, the University of Illinois Medical Center at Chicago will implement a significantly revised medical center policy & procedure (P&P) on the conduct of pharmaceutical sales representatives (PSRs). This P&P was approved by the Medical Staff Executive Committee, Medical Center Management Policy & Procedure Committee, and Pharmacy & Therapeutics Committee. This change is intended to promote an environment that ensures optimal patient care by minimizing interruptions in care and one that respects the integrity and confidentiality of patient privacy.

The complete revised P&P, TX 3.08, can be found on the medical center's intranet page. Some key changes are summarized below.

- PSRs must register with Pharmacy Services and obtain a photo ID badge before they will be allowed to function at the medical center.
- Other pharmaceutical company employees (e.g., manager, medical science liaison) visiting the medical center must obtain a "guest" badge from the Taylor Street/EEI Pharmacy at each visit.
- The ID badge must be worn prominently to allow easy recognition by the UIMCC staff and security. In addition, the representative must obtain a vendor's badge from the reception desk located in the hospital lobby when entering the hospital.
- PSRs are NOT permitted in any patient care areas in the hospital and clinics. This includes conference rooms located in patient care areas in the hospital and clinics.
- PSRs may make appointments and meet with attending physicians and other healthcare

providers in their offices in non-patient care areas (e.g., office in College of Medicine)

- Attending physicians in the Anesthesiology Department and the Emergency Department with private offices only in the hospital may meet with PSRs in their offices. Attending physicians must greet and escort the PSRs from the Hospital Pharmacy administrative office to their private offices.
- The University of Illinois Hospital Formulary is the possession of the medical, nursing and pharmacy staff. PSRs are expected to respect the formulary and not attempt to influence the decisions of the P&T Committee in any way nor the drug therapy decisions of faculty.
- PSRs may not directly fund meals or any type of food in the hospital and clinics.
- Individuals may not accept gifts from a manufacturer having a cumulative total value of more than \$50 annually. Any gifts that are not educational in value or do not directly improve patient care are prohibited (e.g., logo imprinted pens, paper, etc.).
- All PSRs are expected to adhere to the guidelines for ethical practice put forth by the American Medical Association's PhRMA Code on Interactions with Healthcare Professionals.
- Violation of the PSR policy is grounds for disciplinary action.
- The Medical Center seeks to maintain a good working relationship with all visitors and representatives. However, our mission of patient care, research and education, and training must not be compromised.

#### Medical Center Staff Responsibilities

- All UIMCC faculty and staff should be familiar with the policy and monitor PSR activities within the medical center for compliance.
- PSRs not wearing an appropriate badge should be directed to the Taylor Street/EEI Pharmacy for registration prior to the appointment.
- Meet PSRs by appointment only in non-restricted areas (e.g., private office).
- Do not give medical center lists (committee membership, phone, pager numbers, etc) to PSRs.
- Any PSR exhibiting conduct deviating from the policy & procedure should be asked to leave the medical center; all violations of the P&P must be reported to the Hospital Pharmacy administrative office.

#### P & T Formulary Update

##### Additions

- Atazanavir (Reyataz®)
- Caffeine sodium benzoate
- Darunavir (Prezista®)
- Dofetilide (Tikosyn®) – Restricted to 6WSD nursing unit requiring continuous telemetry

monitoring and approved by TIP® registered cardiologist

- Emtricitabine (Emtriva®)
- Emtricitabine/Tenofovir (Truvada®)
- Fosamprenavir (Lexiva®)
- Ibutilide (Corvert®) – Restricted to Cardiac Cath Lab
- Insulin detemir (Levemir®)
- Micafungin (Mycamine®) – Use restricted to criteria for use, see below.

##### Deletions

- Caspofungin (Cancidas®)

#### Micafungin Medication Use Policy

##### Formulary restrictions:

1. Empiric treatment of yeast identified from a blood culture in:
  - a) Immunocompromised hosts (ANC < 500, solid organ or bone marrow transplant recipients, HIV-seropositive status, currently receiving high-dose steroids)
  - b) Clinically unstable patients
  - c) Patient with recent (within 2 months) *C glabrata* infection/colonization
  - d) Patient with recent (within 2 months) azole exposure
2. Alternative for treatment of suspected or proven infections caused by *Aspergillus* species
3. Alternative for empiric antifungal therapy in patients with persistent fever and neutropenia
4. Treatment of fungal infections in patients refractory or intolerant to other antifungal agents, as determined by Infectious Diseases

##### Not to be used for the routine treatment of:

1. Candidemia in low-risk patients or fluconazole-susceptible *Candida* infections
2. Oropharyngeal/esophageal candidiasis
3. Urinary tract infections (<2% of active drug excreted in urine)

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