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Haloperidol (Haldol): Cardiovascular Effects Lead to New Labeling

by Ashley Lowe

The Food and Drug Administration (FDA) recently issued an alert to health care professionals about labeling revisions of Haloperidol. This warning reflects potential cardiovascular effects of the intravenous preparation of haloperidol, such as reports of Torsades de Pointes (TdP) and QT prolongation.

Haloperidol is FDA-approved for the treatment of schizophrenia and for the control of tics and vocal utterances of Tourette's Disorder.¹ High doses are also commonly given intravenously for agitation in intensive care patients. Intravenous use is not approved by the FDA and this indication is considered off-label.

The labeling changes were prompted by the results of two post-marketing investigations conducted by Johnson & Johnson, (the company sponsoring injectable haloperidol products). The investigations were originally requested by Italy's drug regulatory agency (AIFA) and consisted of an evaluation of Johnson & Johnson's Benefit Risk Management safety database.

- The 1st study found 229 reports of all QT prolongation-related adverse events through June 30, 2005
 - 73 reports of TdP
 - 11 cases were fatal and 8 of those patients received at least 1 dose of IV haloperidol
 - Johnson & Johnson attributed the majority of the adverse events to unknown etiologies, potentially confounded by other QT-prolonging conditions
- The 2nd study pertained to adverse cardiac events reported through July 30, 2005 which were associated with the use of the long-acting depot formulation, haloperidol decanoate
 - 13 cases were identified which included QT prolongation, TdP, ventricular arrhythmias, and sudden death
 - Results of the second study were reported to the FDA in March, 2007

According to the AHFS Drug Information resource, many of the reported adverse cardiac events were associated with intravenous haloperidol at doses greater than 35 milligrams per day.³

The FDA is continuing to review adverse events but there are currently no guidelines for the use of high-dose haloperidol. It is therefore very important for health care professionals to take this new information into consideration when making decisions regarding haloperidol therapy, especially in patients with other conditions or drug therapy that may cause prolonged QT intervals

The specific labeling changes with regard to this warning are as follows:

Warnings: Cardiovascular Effects of Haloperidol^{1,4}

- Cases of sudden death, QT-prolongation, and TdP have been reported in patients receiving haloperidol.
- Higher than recommended doses of any formulation & IV administration of haloperidol appear to be associated with higher risk of QT-prolongation and TdP.
- Although cases have been reported even in the absence of predisposing factors, particular caution is advised in treating patients with other QT-prolonging conditions:
 - Electrolyte imbalance (hypokalemia, hypomagnesemia)
 - Drugs known to prolong the QT
 - Underlying cardiac abnormalities
 - Hypothyroidism
 - Familial long QT-syndrome
- Haloperidol injection is not approved for IV administration
 - If administered intravenously, the ECG should be monitored for QT prolongation and arrhythmias

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References

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FDA's New Generic Initiative for Value and Efficiency (GIVE) by Jennifer Nguyen

Generic drugs can cost 30-80% less than their brand-name equivalents.¹ According to the National Association of Chain Drug Stores, in 2004 generic drugs cost an average of \$28.74, compared to \$96.01 for brand-name drugs. With increasing utilization of prescription medications, there is unquestionably a demand for less expensive alternatives.

The Food and Drug Administration's *Orange Book* contains a database of approved drugs along with their therapeutic equivalence ratings. As of June 2005, 11,167 drugs were listed in the *Orange Book*, with 8,400 having generic counterparts. Since an innovator's patent on a brand-name drug can last many years, it is also important that physicians and patients inquire about generic drugs available in the same drug class as a brand-name medication that does not yet have a generic equivalent.

Positive patient compliance with taking prescription medications has been tied to drug affordability. While many patients are grateful for the lower cost of available generic drugs, there is still public misconception in the belief that generic drugs are cheaper because they are inferior to brand name drugs. It is important to understand that differing market forces (including minimal research and development costs, competition among generic manufacturers and substantially lower marketing costs) impact the favorable pricing of generic medications.

On October 4, 2007, the FDA launched the Generic Initiative for Value and Efficiency (GIVE).¹ This initiative addresses the growing market demand for generic drug products brought about by advancements in the medical field and increasing health care costs. GIVE coordinates the efforts of the Office of Generic Drugs (OGD) to increase the efficiency of the drug review and approval process. Its ultimate goal is to increase the number and variety of safe, high-quality generic drug products available to consumers. Approval rates for generic drugs increased by over 30% in 2007, with 682 new generic drugs approved.²

GIVE functions to:¹

- increase the number of applications for generic drug products
- facilitate more efficient and prompt review of abbreviated new drug applications (ANDAs)
- expedite review of applications for which there is high demand for generic equivalents
- recruit and train qualified staff to review ANDAs

Generic drug products must meet the following requirements to be approved:³

- contain the same active ingredients as their brand-name counterparts
- be identical in strength, dosage form, stability, purity, quality, safety, and route of administration
- demonstrate bioequivalency
- have the same indication for use
- meet the same good manufacturing practice regulations of the FDA that are required of innovative products

Generic drug products decrease health care costs and are an important component of health care. Thus, there is a need for optimizing the OGD's management of increasing applications and workload to yield prompt processing of new drug applications. It is hoped that the GIVE initiative will help accomplish this.

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Doribax (doripenem) - A New Drug for Urinary Tract Infections by Amanda Lausen

The FDA approved Doribax (doripenem for injection) in October 2007 for the treatment of complicated urinary tract infections (UTIs), including pyelonephritis.¹ Doripenem is a synthetic antibiotic in the carbapenem class and is structurally related to beta-lactam antibiotics. It has a spectrum of activity that covers aerobic and anaerobic gram-positive and gram-negative bacteria.² Doripenem can be used as a single agent for UTIs caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*.¹

Features of doripenem:³

- Bactericidal activity against most species.
- Post-antibiotic effect of approximately 2 hours in vitro for *P. aeruginosa*.
- Stability to common and extended spectrum β -lactamases.
- Stability to human renal dehydropeptidases.
 - No co-administration with cilastatin needed.
 - Prolonged antibiotic effect.
- Low serum protein binding.
- Minimal risk of convulsive adverse reactions, however, similar kinetic and pharmacodynamic qualities to meropenem.

The recommended dosage of doripenem for complicated UTIs is 500 mg intravenously every 8 hours for 10 days. The duration may be extended to 14 days for patients with concurrent bacteremia. After three days of therapy the patient may be switched to an appropriate oral therapy if the condition shows improvement.² Doripenem is primarily excreted unchanged by the kidneys and the dosage needs to be adjusted for patients with moderate to severe renal impairment. There is no evidence of hepatic metabolism; therefore dosage does not need to be adjusted for patients with hepatic impairment. The use of doripenem during pregnancy or in children has not yet been evaluated.²

When given concurrently with valproic acid, doripenem, like other carbapenems, has been shown to reduce serum valproic acid concentrations, possibly resulting in a loss of seizure control.² Patient's serum levels should be monitored when doripenem and valproic acid are given together and doripenem should be discontinued if therapeutic levels cannot be maintained or seizures develop. Additionally, doripenem should not be administered with probenecid, which interferes with the tubular secretion of doripenem and leads to increased plasma concentrations. Doripenem has not been shown to inhibit or induce any of the major CYP450 enzymes, decreasing the risk of interactions with drugs metabolized via those pathways.²

Doripenem has been shown to be an effective option for the treatment of bacteria strains resistant to other types of therapy.⁴ A phase III multinational study sponsored by Johnson & Johnson compared the efficacy and safety of doripenem with levofloxacin. It included 748 patients who were randomized to receive intravenous levofloxacin or doripenem for 10 days. The end points of the study were cure rates at the test-of-cure visit six to nine days after the patient completed drug therapy. During the trial, patients were allowed to switch to oral levofloxacin if they had received an approved number of doses of the randomized intravenous therapy and met pre-specified criteria. Overall, in comparison to levofloxacin, doripenem was shown to be not-inferior in respect to microbiologic cure rates and the eradication of *E. coli*, *K. pneumoniae* and *P. mirabilis*.⁴ This study also showed that patients diagnosed with a complicated UTI had higher cure rates when treated with doripenem. However, there was no difference in cure rate between doripenem and levofloxacin when treating pyelonephritis.⁴ Adverse event rates were similar for both the doripenem and the levofloxacin groups. The most commonly reported side effects were gastrointestinal disorders and headache.⁴

According to the package insert, common adverse reactions reported with doripenem in phase III clinical trials were headache, nausea, rash, diarrhea, and phlebitis. Patients who discontinued therapy did so most often due to nausea, vulvomyotic infection, and rash. The occurrence of *C. difficile* was less than 1% in all three of the clinical trials. Outside the United States, reports of anaphylaxis, Stevens Johnson Syndrome, toxic epidermal necrolysis, interstitial pneumonia, and seizure have also occurred but the frequency has not been determined.²

Doripenem has also been approved by the FDA to treat complicated intra-abdominal infections. It was previously approved in Japan in September 2005 under the name Finibax for use in the treatment of complicated UTIs and respiratory infections.^{4,5} Currently, other countries are conducting trials to examine doripenem's usefulness as a treatment for nosocomial pneumonia and to further research on its effectiveness for UTIs and intra-abdominal infections.⁴ Table 1 on the following page lists average wholesale prices (AWP) for doripenem and comparable antibiotics. Decisions on antibiotic choice should be based on individual indication and known or suspected pathogens.

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Table 1 Costs of doripenem and comparable antibiotics⁶

Drug	Usual Adult Dose	Comments	Average AWP/day
Doripenem (Doribax)	500mg IV every 8 hours	Spectrum similar to imipenem/cilastatin and meropenem	\$138
Ertapenem (Invanz)	1 gram IV/IM once daily	Spectrum makes it more suitable for community-acquired infections than nosocomial infections No coverage for Pseudomonas or Acinetobacter	\$66
Imipenem/Cilastatin (Primaxin)	500-1000mg IV every 6 to 8 hours	Highest seizure risk Not effective for MRSA	\$118 (500mg Q 8)
Meropenem (Merrem)	500-1000mg IV every 8 hours	Only carbapenem approved for meningitis	\$111 (500mg Q 8)
Levofloxacin (Levaquin)	250mg IV daily (complicated UTI)	Doripenem found non-inferior to levofloxacin for complicated UTI	\$22
Piperacillin/Tazobactam (Zosyn)	4.5 gm IV every 6 hours	Doripenem found non-inferior to piperacillin/tazobactam for nosocomial pneumonia	\$96

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Is Byetta (exenatide) Associated with Pancreatitis? by Carole Kashima

On October 16, 2007, the Food and Drug Administration released a warning on the possible association of acute pancreatitis with the use of Byetta (exenatide), based on 30 reported postmarketing cases of acute pancreatitis in patients treated with the drug. Exenatide is an incretin mimetic agent used as an adjunct to metformin, sulfonyleurea, or thiazolidinedione to enhance glycemic control in patients with type 2 diabetes.

Of the 30 patients, 27 had at least one other risk factor for pancreatitis (e.g. gallstones, severe hypertriglyceridemia, alcohol use). Six patients exhibited worsening symptoms when the dose was increased from 5 mcg twice daily to 10 mcg twice daily. Overall, 21 patients required hospitalization. There were no instances of hemorrhagic or necrotizing pancreatitis reported. However, 5 patients were reported to have experienced other serious complications such as dehydration and renal failure, suspected ileus, phlegmon, and ascites. Of note, discontinuation of the drug led to improved clinical status in 22 of the 30 cases.

Initial trials of exenatide observed mild to moderate adverse effects, with the most common being nausea (44%), vomiting (13%) and diarrhea (13%). Postmarketing data of acute pancreatitis were briefly mentioned in the package insert; however, frequency of incidence is not mentioned as reports were voluntary and from an unknown sample size.

The current FDA recommendation advises health care professionals to instruct patients to discontinue exenatide and seek prompt medical care if they experience symptoms of pancreatitis such as severe abdominal pain which may or may not be associated with vomiting. If pancreatitis is confirmed, exenatide should not be reinitiated unless drug-induced pancreatitis is ruled out.

Amylin Pharmaceuticals, Inc. has agreed to update the “Precaution” section of the exenatide package insert to include the above information about acute pancreatitis.

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