



October 16, 2003

Home > Newsletters > April 2002

- About ASA
- Patient Education
- Clinical Information
- Continuing Education Resources
- Annual Meeting
- Calendar for Meetings
- Office of Governmental & Legal Affairs
- Practice Management
- Resident and Career Information
- Placement Service
- Publications and Services
- Related Organizations
- News Archives
- Links of Interest

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**FDA Alert:
Current FDA Report on Droperidol Status and Basis
for 'Black Box' Warning**

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U.S. Food and Drug Administration*

Anesthesiologists have been using droperidol for years in doses of less than 1 mg and have not been aware of significant complications, according to Bruce F. Cullen, M.D., Vice-President for Scientific Affairs. So recently when the U.S. Food and Drug Administration (FDA) placed stricter warnings on this product due to reported adverse cardiovascular events, Dr. Cullen contacted FDA officials for an explanation. While FDA continues to review all available information on this matter, including ongoing studies, Cynthia G. McCormick, M.D., of the FDA agreed that making information more available to the anesthesiology community was in order and supplied the following article exclusively for the ASA NEWSLETTER. Comments about droperidol can be directed to FDA at www.fda.gov/cder/audiences/acspage/anestheticroster1.htm.

This brief report will summarize the factors leading to the Food and Drug Administration's (FDA's) action to place additional warnings on droperidol labels that highlight the risk of QT prolongation and torsades de pointe (TdP), a serious and sometimes fatal arrhythmia. Droperidol is a butyrophenone approved in 1970 as an injectable formulation for the reduction of nausea and vomiting associated with surgical and diagnostic procedures. It also has been widely used off-label for the treatment of acute mania in the psychiatric emergency setting. Droperidol is only available in the United States as an injectable formulation in a concentration of 2.5 mg/mL. The current recommended initial dose for adults is 2.5 mg intramuscularly or intravenously (I.V.). In the current anesthetic setting, doses of 0.625 mg and lower are in frequent use, but these doses have never been shown to be safe and effective in an application to the FDA.

While the labeling for droperidol carried warnings about the potential for cardiovascular adverse events at high doses and in the setting of alcoholic withdrawal, these warnings did not reflect what had been reported to FDA over the years since the product's initial marketing or in the world literature. In January 2001, following notification that droperidol was being discontinued from worldwide markets, FDA began to re-examine its databases for evidence of cardiovascular adverse events reported in the United States and globally. In June 2001, FDA concluded that the available information confirmed a

FEATURES

2001 ASA Annual Meet
Foundations Are Stron

- A Future Without R
No Future at All
- Guinea Pigs, Big Id
the Glory of Regula
- APSF Research Pr
- AHRQ Grants Plac
Members on Cuttin
Safety Research
- Got Funds? NIH Dc
- IARS Wants You
- A Strong Foundati
Research Starts He
- First FAER Honora

ARTICLES

- FDA Alert: Curr
Report on Drop
Status and Bas
'Black Box' Wai
- Orlando--A Story Si
Written
- Plans Under Way fr
ASA Annual Meetir
Orlando
- Climbing to Succes
Postgraduate Medi
Training in Anesthe
KCMC
- Already a Busy Yea
Committee on Phys
Resources
- MHAUS to Offer W
Award

greater cardiovascular risk than was previously appreciated.

Examination of all available spontaneous adverse event reports revealed approximately 100 unique reports of cardiovascular events of which there were approximately 20 unique reports of TdP and/or QT/QTc prolongation. Tabulation of selected cases from the FDA database and the sponsor's worldwide database revealed at least 38 cases of cardiovascular events of which there were 25 cases of cardiac or sudden death and nine cases of TdP with the remainder ventricular extrasystole or syncope. This subset of 38 cases was selected for careful review due to the completeness of the information, such as information on concomitant drugs, time of onset and specificity of report. Eleven cases reported an onset time of 30 minutes or less following drug administration.

Of 28 out of 38 cases in which dose was reported, 12 cardiovascular adverse events occurred at doses at or below 2.5 mg. These included reports of TdP (three cases), cardiac arrest (three cases) and death (four cases). At doses below 1 mg, there were five reports, including one death, one cardiac arrest and one TdP. The maximum QT interval reported in this group was 600 msec in a patient receiving a single dose of 0.625 mg of droperidol. This patient also experienced nonfatal TdP.

Spontaneous reports of adverse events associated with a drug that has been marketed for more than 30 years can be expected to be very limited. Therefore, the number of reports passively received does not necessarily reflect the magnitude of the problem but reflects only a fraction of the total number of events. Since the total extent of exposure is also not known once a drug is marketed, calculation of true incidence is not possible because neither the actual total number of events nor the total extent of exposure is known. In the case of droperidol, the finding of a dose-dependent prolongation of the QTc of the magnitude described in the German literature, coupled with actual reports documenting TdP at and below the labeled dose, was considered a serious risk, one with no margin of safety.

Information from clinical trials in the published medical literature supports the long-held belief that droperidol prolongs the QTc interval length in a dose-dependent fashion. Two of these beliefs bear mentioning.

In a German prospective study³ designed to explore the relationship between dose of droperidol and QTc prolongation, 40 patients undergoing head and neck surgery were randomized to one of three dose groups receiving 0.1, 0.175 and 0.25 mg/kg, respectively. Significant prolongation of the median QTc was found in all three I.V. droperidol dosing groups compared to their baseline control. The medians of the maximum increases in QTc intervals seen in a dose-dependent manner were: 37 msec at 0.1 mg/kg (n=10); 44 msec at 0.175 mg/kg (n=10); and 59 msec at 0.25 mg/kg (n=20). These findings were measured to only 10 minutes, but the increases were seen after one minute.

A French case report⁴ exploring the association between TdP and droperidol described a patient with no risk factors for cardiovascular disease and no history of QT prolongation who developed TdP with loss of consciousness following a 12.5-mg I.V. dose of droperidol. Upon rechallenge, she had a similar episode lasting 10-45 seconds

- Anesthesia Founda
Paying It Forward
- ASA Patient Safety
Videotapes Contin
Available

DEPARTMENTS

- Ventilations
- Administrative Upd.
- Washington Report
- Practice Managem
- State Beat
- Subspecialty News
- What's New in...Ar
- What's New in...Ar
- Residents' Review
- Spotlight on...
- ASA News
- In Memoriam
- Component Society
- Letters to the Edito
- FAER Report

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without loss of consciousness. The episode was followed by a run of ventricular tachycardia that responded to electrical cardioversion. Following this report, a small study was undertaken. This study reports electrocardiographic (ECG) changes in 55 patients (22 with cardiac history). All received droperidol 0.25 mg/kg I.V. before surgery and had ECGs at baseline and serially for 10 minutes following droperidol. The authors report a significant increase in QT above baseline for 70 percent of patients by the end of the first minute. QT increased from 387 ± 34 msec to 423 ± 37 msec, and the QT/QTc ratio increased from 1.06 ± 0.08 to 1.28 ± 0.1 . QTc changes were not directly reported.

While both of these reports involved higher doses than are currently used in the anesthetic setting, they point out two important features. First, there is a dose-response relationship between droperidol administration and QTc prolongation, and next, the QT prolongation can recur upon rechallenge with droperidol. These reports implicate droperidol in these cardiovascular adverse events.

The FDA held many internal meetings involving senior management to discuss these findings, particularly in the context of other drugs that have shared this characteristic, comparing this signal with other similar drugs. The FDA conveyed its cardiovascular safety concerns with representatives of Taylor Pharmaceuticals of Akorn, Inc., the U.S. holder of the marketing application for droperidol injection. In response to these concerns, the firm proposed revised labeling for a maximum initial adult dose of 2.5 mg or less and inclusion of a "black box" warning.

Because of the serious nature of the reported cardiovascular adverse events associated with droperidol use and the fact that they were associated with doses below the labeled dose, the FDA sought a conservative but definitive means to warn the prescribing public of this information. The FDA has used the black box warning for other drugs posing similar adverse cardiovascular risk with relatively few reported cases and more widespread use. Factors that were taken into consideration in implementing the black box warning included the fact that warnings about cardiovascular toxicity had already been in the package insert for many years. The existing warnings understated the risks in that the described events were reported to occur even at doses below those approved.

The outcome of the FDA meetings was that the administration committed itself to conducting a definitive pharmacokinetic/pharmacodynamic study to evaluate the effect of dose on the QTc interval, exploring doses from placebo to 0.625 mg, 2.5 mg and 5.0 mg in a crossover design in healthy volunteers who would be on no concomitant medications. This study is ongoing and is expected to be completed later this year. Concurrently, examination of alternative medications and their adverse effects is being conducted by the administration. The FDA continues to monitor droperidol adverse event reports very closely for any new or stronger signals of risk associated with droperidol use.

At the point at which the FDA has reviewed these materials and the results of the cardiovascular study, it plans to convene a meeting of the Anesthetics and Life Support Drugs Advisory Committee to consider and weigh all of the available information and discuss possible future actions. In the interim, we are working with the manufacturer of droperidol to inform practitioners of the new findings

and facilitate careful management of patients to prevent untoward events related to QT prolongation from occurring.

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