

Inside the black box: current policies and concerns with the United States Food and Drug Administration's highest drug safety warning system

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Purpose of review

To evaluate the United States Food and Drug Administration use of the black-box warning system to promote drug safety and to examine the droperidol black-box warning as a case study.

Recent findings

Scientific studies report that there is no basis to issue a black-box warning for perioperative administration of droperidol for postoperative nausea and vomiting on the basis of the potential of adverse cardiac events (prolongation of the QT interval and/or development of torsades de pointes).

Summary

Rather than relying on well conducted clinical investigations, the Food and Drug Administration subjectively issued a black-box warning to droperidol, which effectively removed droperidol from clinical practice for the indication of postoperative nausea and vomiting. Newer data suggest that the incidence of prolongation of the QT interval and the occurrence of torsades de pointes is similar to more expensive alternative medications used to treat postoperative nausea and vomiting.

Keywords

droperidol, drug safety, postoperative nausea and vomiting, QT interval, torsades de pointes

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Introduction

Initiated in 1862 as a one-person office, the United States Food and Drug Administration (FDA) is currently an agency of the Department of Health and Human Services of the United States (US) federal government. With 11 000 employees and an annual budget greater than 2.5 billion dollars, the FDA regulates 1.5 trillion dollars of goods accounting for 25 cents (\$0.25) of every dollar spent by consumers in the USA [1•]. The primary areas of the agency's oversight include pharmaceuticals for humans and animals, biological products, food supply, medical devices, radiation-emitting devices and cosmetics. Drug safety is a major focus of the FDA. Originally, the FDA possessed little regulatory power; however, it is currently an organization with global responsibilities, a complex drug approval process and significant control over a major segment of the US economy. As the governmental watchdog for drug safety, the FDA evaluates the profile of a drug using various data sources to determine whether the drug's benefits outweigh its risks. If the drug is approved for the general public, the FDA requires pharmaceutical companies to list all of the drug's side effects on its labeling and uses various visual methods to

communicate increasingly dangerous and preventable risks to doctors and their patients [1•].

The black-box warning system

The black-box warning (BBW), the highest level of all drug warnings promulgated by the FDA, highlights the most serious adverse reactions and potentially life-threatening side effects [1•]. The legal foundation for the BBW is established in regulations issued by the FDA in 1979, which mandated format and content for prescription drug labeling in the USA [2•]. In these regulations, the use of a 'boxed warning' (BBW) is noted [1•,2•,3,4].

Special problems, particularly those that may lead to death or serious injury, may be required by the FDA to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data.

The BBW is the most visually prominent information on the package insert. The BBW information is bolded and surrounded on all four sides by a solid black line in an

effort to draw the prescriber's attention to the warning [1**]. If a boxed warning is required, its location will be specified by the FDA [2**]. The warning indicates that the FDA deems the boxed information to be essential to proper prescription or aids the physician in monitoring for severe adverse effects.

A BBW warning is used in the following three situations [5].

- (1) 'There is an adverse reaction so serious in proportion to the potential benefit from the drug that it is essential that it be considered in assessing the risks and benefits of using the drug. This includes potentially life-threatening or permanently disabling adverse reactions.
- (2) There is a serious reaction that can be prevented or reduced in frequency or severity by patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing the patient in a specific manner or avoiding use in a specific clinical situation.
- (3) The FDA approved the drug with restrictions on use and distribution to assure safe use.'

Although the FDA has published this general guidance as to conditions that result in a BBW, it has not objectively defined a specific protocol that it utilizes to issue a BBW [2**,5]. However, Beach *et al.* [6], on the basis of their own research, defined the circumstances in which a BBW is likely to be issued:

- (1) early detection of a side effect by physicians may result in intervention that may reverse the adverse reaction;
- (2) a well defined subset of patients are at higher risk for the treatment;
- (3) the risk from the treatment of the particular drug may outweigh the benefits in particular circumstances;
- (4) the dosing or drug interaction is pivotal to the risk;
- (5) the training of the physician or the setting is crucial; and
- (6) there are other special requirements for administering the drug.

The issuance of a BBW has numerous implications for patients, physicians and the pharmaceutical companies. For patients, a BBW may require choosing a drug that is not only more expensive, but may also be associated with its own unique safety profile set of adverse reactions. For doctors, owing to inconsistencies in the BBW system and the language and methods by which this information is communicated, the warning may be disregarded by the busy practitioner [2**]. For the pharmaceutical companies, the combination of marketing prohibitions, increased litigation and negative media attention typi-

cally leads to a decrease in sales. Because of this effect on sales, drug companies often resist altering the package labeling, especially for those with patent rights that generate significant revenue for the company.

Theoretically, the BBW system is the perfect way to provide access to the most effective treatments while maintaining patient safety. However, the BBW process may be flawed, based on the information on which FDA Drug Advisory Committees support their decisions and on the methods by which they communicate their findings. The nonspecific and arguably unscientific methods by which a drug receives a BBW, in addition to biases of committee members making critical decisions regarding the fate of dangerous drugs, have cast doubt on the quality of the system [6]. The process of BBW is as follows:

- (1) the BBW is a subjective designation;
- (2) there is no standardized objective process for BBW designation;
- (3) the BBW does not require peer review;
- (4) the process is based on:
 - (a) clinical data
 - (b) animal data;
- (5) a pharmaceutical company cannot apply a BBW unilaterally to a drug.

The droperidol black-box warning: a case study

In 2001, 31 years after its approval, the FDA issued a BBW for droperidol based on individual safety reports of adverse events hypothesized to be related to prolongation of the QT interval and the development of torsades de pointes (TdP) [7] (Fig. 1). The FDA evaluated 273 adverse event communications received during the study period (1997–2002) [8–10,11**,12*,13*] (Fig. 2). Of note, 74% of reports were from outside the USA. The majority of deaths contained in the database were associated with large doses of droperidol (25–250 mg). In addition, when duplication of reporting of adverse cardiac events (ACEs) is taken into account, only 65 reports are verified. (Note, Jackson *et al.* [9] used a slightly larger denominator of reported cases (277) rather than the more commonly reported 273 cases.) Detailed analysis of the case reports in the FDA droperidol database reveals significant confounding factors; for example, multiple medications, including those which also increase QT interval, multi-organ dysfunction and large droperidol doses used in psychiatric patient populations, such that a conclusion as to the precise cause of the reported dysrhythmias cannot be definitively established [13*]. Given this variability in reporting and the complexity of the cases, only five of 273 cases were associated with droperidol doses of 2.5 mg or less and presented with ventricular tachycardia

Figure 1 Black box warning issued for droperidol by the United States Food and Drug Administration

WARNING

Cases of QT prolongation and/or torsade de pointes have been reported in patients receiving droperidol at doses at or below recommended doses. Some cases have occurred in patients with no known risk factors for QT prolongation and some cases have been fatal.

Due to its potential for serious proarrhythmic effects and death, droperidol should be reserved for use in the treatment of patients who fail to show an acceptable response to other adequate treatments, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs (see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS).

Cases of QT prolongation and serious arrhythmias (e.g., torsade de pointes) have been reported in patients treated with droperidol. Based on these reports, all patients should undergo a 12-lead ECG prior to administration of droperidol to determine whether a prolonged QT interval (i.e., QTc greater than 440ms for men or 450ms for women) is present. If there is a prolonged QT interval, droperidol should **NOT** be administered. For patients in whom the potential benefit of droperidol treatment is felt to outweigh the risks of potentially serious arrhythmias, ECG monitoring should be performed prior to treatment and continued for 2–3h after completing treatment to monitor for arrhythmias.

Droperidol is contraindicated in patients with known or suspected QT prolongation, including patients with congenital long QT syndrome.

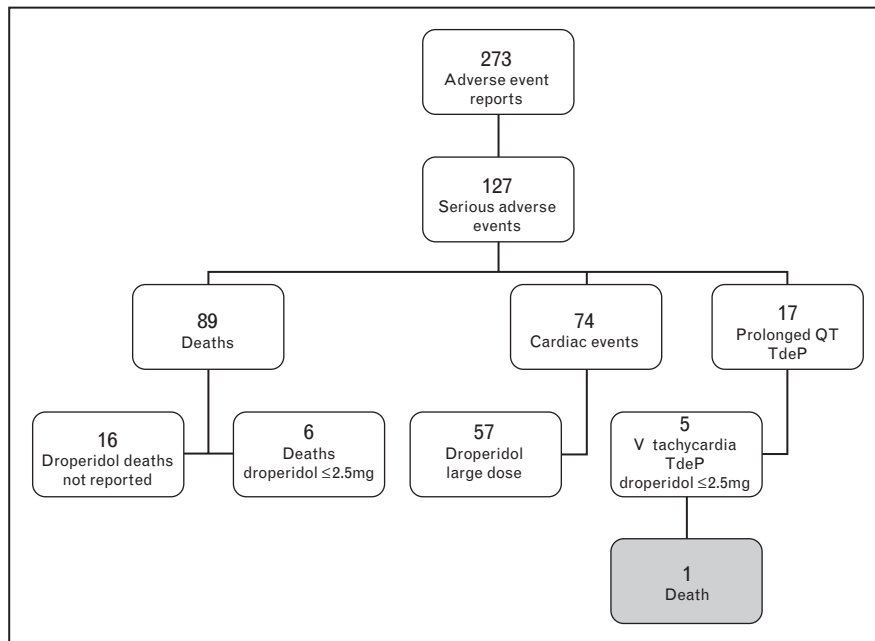
Droperidol should be administered with extreme caution to patients who may be at risk for development of prolonged QT syndrome (e.g., congestive heart failure, bradycardia, use of a diuretic, cardiac hypertrophy, hypokalemia, hypomagnesemia, or administration of other drugs known to increase the QT interval). Other risk factors may include age over 65 years, alcohol abuse, and use of agents such as benzodiazepines, volatile anesthetics, and intravenous opiates. Droperidol should be initiated at a low dose and adjusted upward, with caution, as needed to achieve the desired effect.

Reproduced from [7].

or TdeP (Fig. 2). This represents one fatality possibly related to droperidol in 4 years of data collection when between 11 million and 25 million doses of the drug were sold annually [11^{**},13^{*}]. The FDA's decision to attach a BBW to droperidol may have also been triggered by a

decision from the manufacturer, Janssen-Cilag Ltd, to discontinue producing the drug based on the United Kingdom's drug regulatory agency's (which was at the time called the Medicines Control Agency) concerns regarding ACE. However, these ACEs were associated

Figure 2 Summary of data submitted to the United States Food and Drug Administration for adverse events related to droperidol administration



The reports (n = 273) were collected from 1997 to 2002. TdeP, torsades de pointes; V tachycardia, ventricular tachycardia. Data based on [10].

with high doses of an oral preparation, not the intravenous preparation and its lower dose range. Regardless, the company removed all formulations of droperidol from the market [12*].

The FDA utilizes increases in the QT interval as a proarrhythmic marker for TdEP in regard to the droperidol BBW. Roden [14**] notes that the single most common cause of restriction or withdrawal of the drug from the market by the FDA is prolongation of the QT interval associated with polymorphic ventricular tachycardia or TdEP. FDA representatives state that current evaluation of new drugs tests for their effect on cardiac repolarization (prolongation of QT interval) as well as hepatic toxicity [15]. According to Kao *et al.* [12*] and Habib and Gan [11**,16*], prolongation of the QT interval is a surrogate marker for arrhythmogenicity, as TdEP is very uncommon and difficult to assess. Further, uniform agreement on the methodology for measurement of the QT interval is lacking (e.g. use of direct QT interval measurement vs. corrected QT intervals for heart rate or R-R interval, etc.). There is general agreement by investigators that droperidol causes increases in the QT interval in the perioperative period. TdEP is associated with an increase in the QT interval. But no link has been established between increased QT interval and incidence of TdEP in the perioperative period for droperidol administration [13*,16*]. Two studies deserve special mention. Domino *et al.* [17**] performed a meta-analysis involving 7324 patients enrolled in 54 prospective, randomized, double-blind investigations. In comparison with droperidol, ondansetron and metoclopramide, both droperidol and ondansetron were equally effective for postoperative nausea and vomiting (PONV) and the overall risk of adverse events did not differ between the two drugs. Metoclopramide was least effective. Nuttall *et al.* [18**] evaluated perioperative droperidol administration in a large group of surgical patients ($n = 291\,188$ patients) for QT prolongation or TdEP before (2321 patients) and after (2207 patients) the issuance of the droperidol BBW. From their data, which assessed patient records for the presence of prolonged QT interval or TdEP within 48 h of surgery, they report an incidence of QT prolongation of 1.66% before and 1.46% after the BBW. These data, which reflect a decline of use from 12 to 0% before and after the BBW, respectively, also document that the perioperative ECG abnormalities are seen at a similar incidence even in the absence of droperidol. Similarly, based on their review of the literature, Kao *et al.* [12*] conclude, '...that although droperidol, as other 5HT₃ agonists, increases the QT interval, however clinically significant cardiovascular events seem to be rare'.

In 2001, at the time of the issuance of the BBW, the cost of droperidol (2.5 mg), ondansetron (4 mg) and granise-

tron (1 mg) was \$1.28, \$20.87 and \$36.75, respectively [13*]. There was a 10-fold decrease in droperidol use in the USA in the first year following the BBW. Nuttall *et al.* [18**] note that at their institution, one of the largest academic medical centers in the USA, the use of droperidol for PONV declined from 12% of postoperative patients to zero. In a survey of attendees at a Society of Ambulatory Anesthesia meeting ($n = 295$ responders/1179 registrants), Habib and Gan [19*] reported a significant reduction in droperidol use before and after the BBW for first-line PONV prophylaxis (47–5%) and treatment (38–8%); 92% of responders did not believe the BBW was justified. The reasons for the decrease are likely linked to the intense use of resources required for droperidol administration for PONV. First, droperidol is now a second-line or third-line drug. Second, a 12-lead ECG must be obtained before droperidol administration and the QT interval measured (Fig. 1). ECG monitoring should be used before and for 2–3 h after droperidol treatment. In sum, although being the least expensive alternative by cost, the amount of resources required and a potential extended stay in the postanesthesia care unit and risk of litigation have resulted in very limited use of droperidol.

Lastly, concerning the droperidol BBW, there is an issue of linguistic uncertainty. The opening sentence of the droperidol BBW states (*italics added*) (Fig. 1) [7]

Cases of QT prolongation and/or torsades de pointes have been reported in patients receiving droperidol at doses at or below recommended doses.

Ludwin and Shafer [20**], in support of the droperidol BBW, state that this refers to a 'historical observation' and not to the actual recommendation contained in the BBW. They conclude that the BBW should contain the statement 'Doses of Inapsine below 2.5 mg are considered off-label. The FDA has no position on the safety or efficacy of doses below 2.5 mg.' Rappaport [21], representing the FDA, replied that the droperidol BBW refers only to recommended doses (even though the phrase '... below recommended doses' is included in the BBW). He continues that the FDA is aware of studies utilizing lower doses of droperidol, but these data have not been submitted to the FDA for formal review and approval at this lower dose. A nuance of the system is that, in addition to new drug approval, a pharmaceutical manufacturer must submit data to the FDA regarding toxicity and efficacy in specific doses. In order to approve droperidol at this lower dose, the manufacturer must resubmit data to the FDA for approval. Akorn, the manufacturer of generic droperidol, does not want to incur the expense of the review [20**].

A consensus panel describes the critical effect of the droperidol BBW on the treatment of PONV, which

stated, 'If it were not for the "black box" warning, droperidol would have been the panel's *overwhelming* (italics added) first choice for PONV prophylaxis' [22^{••}]. The panel also noted after an exhaustive review of the literature that '... there has not been a single case report in a peer reviewed journal in which the doses used for the management of PONV has been associated with QTc prolongation, arrhythmias or cardiac arrest'. The American Society of Anesthesiologists (ASA) considers this issue to be so important that an Ad Hoc Committee was created to re-examine newer scientific evidence and, based on their findings, request from the FDA a reconsideration of the BBW for droperidol [23].

Conclusion

The reason for examining the droperidol BBW saga is three-fold. First, to understand the weaknesses in this aspect of the drug review and safety process of the FDA. Second, to restore the use of droperidol to clinical practice by removing the BBW. Third, to have physicians become more proactive in the drug safety process. As drug development becomes more complex and risk-benefit profiles more intricate, the FDA will face new dilemmas regarding drug safety. The FDA's ability to utilize resources and authority granted by new legislation, the 2007 Food and Drug Amendments Act, gives the agency the means to reestablish its place as a leader in innovative scientific approaches to drug evaluation and safety.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 438).

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