Is droperidol escaping the black box?

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It has been suggested that postoperative nausea and vomiting (PONV) is more debilitating than postoperative pain and results in extensive morbidity. Stimuli for nausea and vomiting are multifactorial. The necessity for multimodal antiemesis, and the efficacy of different pharmacotherapeutic agents, is thus riddled with debate and controversy.

It is worth noting that the 2003 Consensus Guidelines for postoperative nausea and vomiting stated that “if it were not for the black box warning, droperidol would have been the panel’s overwhelming first choice for PONV prophylaxis”.

Discovered by Janssen Pharmaceutica in 1961, droperidol is a butyrophenone, and a potent dopamine (D2) receptor antagonist with some histamine and serotonin antagonist activity. Droperidol effectively reduces postoperative nausea in adults in doses as low as 0.625 mg.

At the time of regulatory approval, in 1970, the package insert recommended a starting dose of 2.5 mg. No human pharmokinetic studies had been undertaken on droperidol at this time.

There were reports of QT prolongation with droperidol use in the 1990s. Janssen, in a knee jerk reaction, withdrew droperidol from markets outside the USA in March 2001.

In December 2001, the FDA mandated that the manufacturer of droperidol (Akorn Pharmaceuticals) place a “black box” warning regarding the risk of serious arrhythmogenic effects (e.g. torsade de pointes) and even death after administration of droperidol.

There was an array of risk factors for prolonged QT interval and a multitude of anaesthetic drugs that may induce such arrhythmias.

Furthermore, the literature is abundant with arguments regarding the dose correlation of droperidol with prolonged QT. At the 2003 Advisory Committee meeting, the primary FDA medical office responsible for droperidol labelling stated that “the boxed warning really is not about doses of droperidol < 2.5 mg because the use at doses < 2.5 mg is off-label.”

While the necessity for control of harmful drugs, and the FDA effort to enforce this, is not debatable, the risk versus benefit of an intervention to an individual relies on the art of therapeutics and thorough knowledge of both the drug and the patient in question. It is clearly not a case of “black and white” and, arguably, putting interventions into “boxes” is oversimplifying therapeutics.

References

1. Gan T, Sloan F. How much are patients willing to pay to avoid postoperative nausea and vomiting? Anaesth Analg. 2001;92(2):393–400.