UAMS Journal Club Summary
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Adverse Event Rates of Droperidol vs Standard Therapy

Clinical Bottom Line

Droperidol does not have increased rates of adverse events compared to standard therapy regimens such as haloperidol, midazolam and olanzapine. However, the exact rates of adverse events is difficult to characterize based on the limited data available since previous studies have overall small sample sizes for detecting low frequency events. Evidence suggests that Droperidol does prolong the QT interval in a dose-dependent relationship. However, there is not sufficient evidence to establish a causal relationship between Droperidol and Torsades de Pointes / sudden death. Clinicians should use caution in administering Droperidol in large doses, administration to elderly patients, patients with known structural heart disease, patients with baseline prolonged QT interval, patients on other medications that can prolong the QT interval.

PICO Question

P- adults presenting to the ED
I- droperidol
C- routine therapy (e.g, haloperidol, midazolam, olanzipine)
O- adverse events

Background

Droperidol is an antidopaminergic agent similar to haloperidol used to treat a variety of conditions including agitation, nausea, vomiting and headache. Due to concern for QT prolongation and risk of developing Torsades de Pointes, it received a black box warning by the FDA in December 2001. The pharmaceutical company who originally marketed Droperidol announced a cessation in production due to the proposed risks and supplies were expected to become unavailable. However, many facilities around the world have continued to use the agent and it is becoming more widely available once again. There is debate amongst physicians regarding the evidence that Droperidol should have received a black box warning in the first place. There was little evidence showing increased rates of adverse events compared to other frequently used medications prior to the designation by the FDA. Additionally, there are numerous medications prescribed on a regular basis which have also been shown to contribute to QT prolongation. The severity of QT prolongation that actually contributes to significant clinical events is unclear as well. Ultimately, many physicians argue that adverse event rates for Droperidol are minimal and it should be available for clinical use.

Study 1

Khokar MA, Rathbone J. *Droperidol for psychosis-induced aggression or agitation*. Cochrane Database of Systematic Reviews 2016, Issue 12. Art. No.: CD002830.

Pubmed link: https://www.ncbi.nlm.nih.gov/pubmed/27976370

Validity Rating: overall low risk of bias according to GRADE system

The Basics:
Systematic review of randomized controlled trials (RCTs) in which Droperidol was compared to placebo or standard therapies for treatment of patients with acute aggression/agitation. Outcome measures included resolution of presenting symptoms and adverse events. Six studies were included which included Droperidol vs placebo, Droperidol vs haloperidol, Droperidol vs midazolam and Droperidol vs olanzapine.

Inclusion Criteria:
- Randomized controlled trials
- Adults with psychosis

Exclusion Criteria:
- Non-randomized studies
- Study subjects were not experiencing psychotic illnesses

Primary Outcomes:
- Tranquilization
- Adverse events which varied between studies but generally included arrhythmia, respiratory depression and CNS depression

Follow Up:
Data was collected using the Cochrane Schizophrenia Group's register of Trials which is compiled via major publication resources. Only a single included study was rated as high risk for attrition bias.

Results:
Droperidol provides greater tranquilization compared to placebo with no evidence of increased rates of cardiovascular or respiratory events. Droperidol provides more rapid tranquilization compared to haloperidol with no evidence of increased cardiovascular hypotension or desaturation. Droperidol provides less rapid tranquilization in the first few minutes compared to midazolam with no statistically significant different in adverse events. While not statistically significant, the midazolam group did require occasional airway management. Droperidol had no clear difference in tranquilization compared to olanzapine with no evidence of increased cardio vascular arrhythmia or airway compromise. However, the relative risk for each of the studies had large confidence intervals, likely due to the overall small sample size.

Limitations/Bias:

- Sample sizes are not large enough to adequately detect low frequency events
- Included studies limited to those with acute psychosis which could limit generalizability
- There was significant heterogeneity between the six studies included in the review

Study 2

Kao LW, Kirk MA, Evers SJ, Rosenfeld SH. *Droperidol, QT prolongation, and sudden death: what is the evidence?*. Ann Emerg Med. 2003 Apr;41(4):546-58. doi: 10.1067/mem.2003.110. Review. PubMed PMID: 12658255.

Pubmed link: https://www.ncbi.nlm.nih.gov/pubmed/12658255

The Basics: This was a review article that looked for publications to evaluate if there was evidence for a causal relationship between Droperidol, QTc prolongation, Torsades de Pointes and sudden death. A new FDA black box warning for Droperidol inspired this article. The black box warning was put in place after MedWatch reports of deaths and other cardiac events in patients who had been administered Droperidol. This black box warning was rather atypical because it occurred 31 years after the initial release of the drug.

Methods: Searches performed on EMBASE, MEDLINE, and International Pharmaceutical Abstracts Database with subject headings: “Droperidol,” “Torsades de Pointes,” “Sudden death,” “arrhythmia,” and “QT prolongation.” Due to the small number of available studies, the authors were unable to perform a true systematic review. The reviewed every article found during their search. The authors also reviewed data available from the MedWatch reports.

Results: This was a literature review to evaluate for a causal relationship between Droperidol, QTc prolongation, Torsades de Pointes and sudden death. The authors found 3 human studies and 1 abstract evaluating the relationship between Droperidol and QT prolongation. They also found 7 case reports.

The first study, Lischke et al evaluated QT intervals pre and post IV Droperidol administration prior to anesthesia for elective surgery. All 40 patients had a baseline normal QT interval and none of the patients had a history of cardiac disease. The patients were administered either 0.1, 0.175, or 0.25 mg/kg and serial EKGs were obtained up to 10 minutes after administration. Each group experienced an increase in their baseline QT intervals, which was dose-dependent. Each group experienced an average increase in their QT interval by 37, 44, and 59 ms respectively. No dysrhythmias occurred.

The second study, Guy et al was a prospective, observational study in which 55 patients received 0.25 mg/kg Droperidol before elective surgery. Serial EKGs were obtained up to 10 minutes after infusion. 22 of the 55 patients had known cardiovascular disease. The authors found a statistically significant increase in QT 378±34 ms to 411±38 ms. No dysrhythmias occurred.

Reilly et al was the third human study. It was an observational study that looked at the point prevalence of EKG abnormalities in psychiatric patients. Patients were excluded if they had any medication changes within two weeks. 8% or forty of the patients studied had prolonged QT intervals. Factors associated with prolonged QT intervals were age > 65, TCA use, thioridazine use, and Droperidol use. 37 patients in this study were treated with droperidol and 6 had prolonged QT intervals. Data were missing on 4 patients treated with droperidol.

The authors provided further information on the human abstract study, case reports, and MedWatch data. A common theme among cases was that many of the patients were administered doses much higher than the typical dose used in the emergency department. In addition, in many of the cases patients had pre-existing heart conditions, baseline prolonged QT interval or were on other medications that could prolong the QT interval.

Despite a thorough literature review, the authors were unable to find any high quality evidence to suggest a causal relationship between Droperidol and Torsades de Pointes / sudden death. The data available does demonstrate a dose-dependent relationship between Droperidol and prolonged QT interval.

Limitations/Bias: The major limitation of this article is the lack of data available to perform a true systematic review.