Published in final edited form as:

Intensive Care Med. 2016 November ; 42(11): 1818–1819. doi:10.1007/s00134-016-4512-3.

The Use of Low-Dose IV Haloperidol is Not Associated with QTc Prolongation: Post-hoc Analysis of a Randomized, Placebo-Controlled Trial

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Keywords

haloperidol; QTc interval prolongation; delirium; intensive care

Dear Editor:

Haloperidol is commonly used in the ICU, and at increasingly lower doses, to treat and prevent agitation and delirium.[1] Rate-corrected QT-interval (QTc) prolongation, a well-established risk factor for Torsades de pointes (TdP), frequently occurs in the critically ill.[2] Current product labeling for IV haloperidol includes a warning for QTc prolongation and TdP and all hospital medication systems are programmed to detect drug interactions that might prolong the QTc. Therefore, ICU clinicians remain vigilant in addressing this cardiovascular risk when making haloperidol prescribing decisions and routinely monitoring the QTc after haloperidol has been initiated. While IV haloperidol has been associated with QTc prolongation in retrospective studies when administered at a high daily dose (20 mg) [3, 4], the association between lower-dose IV haloperidol and QTc prolongation remains unclear.

We conducted an IRB-approved, post-hoc analysis of mechanically ventilated, critically ill adults [age = 60 ± 16 years, APACHE-2 score = 20 (17–23), medical =71%] with subsyndromal delirium and a baseline QTc < 500 msec who were randomized to receive haloperidol (H) 1mg IV q6h (n=34) or placebo (P) (n=34) in a double-blind fashion until delirium, 10 days of therapy, ICU discharge, or QTc prolongation (500 msec and/or an increase 60 msec above baseline not attributable to the use of non-haloperidol QTc

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Conflicts of Interest: The authors declare that they have no conflict of interest.

prolonging medications) occurred.[5] Patients with potential underlying risk factors for QTc prolongation were not excluded. The QTc was evaluated every 12 hours by a telemetry strip and confirmed with a 12-lead ECG if prolongation was detected.

Both the baseline QTc (430 ± 32 msec H vs. 421 ± 39 msec P, $p = 0.26$) and average maximum QTc over the course of the study (457 ± 40 msec H vs. 466 ± 39 msec P, $p = 0.34$) were similar between the two groups. The average rate of change over time of the QTc was similar between groups (-0.16 msec/hr H vs. -0.11 msec/hr P, $p = 0.70$). (Figure 1) Between groups, the difference in the proportion of patients who developed QTc prolongation [8/34 (24%) H vs. 14/34 (41%) P, $p=0.19$], a QTc ≥ 500 msec alone [4/34 (12%) H vs. 3/34 (9%) P, $p=1.00$], or an increase in the QTc ≥ 60 msec alone [6/34 (18%) H vs. 14/34 (41%) P, $p=0.063$] were similar. A log-rank test comparing Kaplan-Meier curves revealed the percentage of H and P-group patients free of QTc prolongation was similar across all study days ($p=0.33$).

Using a rigorous study design and including patients with potential underlying non-H-related risk factors for QTc prolongation, we report the use of low-dose IV haloperidol in a mixed population of critically ill adults is not associated with QTc prolongation. Our results, while requiring confirmation in larger cohorts and in patients receiving slightly higher daily IV haloperidol doses (e.g., 8mg), suggest additional QTc monitoring may not be required after low-dose IV haloperidol is initiated in the ICU.

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Haloperidol*	34	33	27	22	12	5	4	4	3	2	0
Placebo*	34	34	31	28	21	14	9	7	6	4	4

Fig. 1.

The average rate of change of the QTc interval as a function of time over the course of the study period was similar between the haloperidol (filled triangles) and placebo (open boxes) groups ($p = 0.70$). *Number of patients receiving study medication on each study day.