Cardiotoxicity of intravenous haloperidol – an update

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Background: The use of haloperidol is compromised by the provocation of cardiac arrhythmias including QT interval prolongation (QTP) leading to polymorphic ventricular arrhythmias, known as Torsades-de-pointes (Tdp). These adverse drug reactions (ADRs) were reported more frequently after intravenous application of haloperidol than after other routes of administration. In 2007, the FDA issued a warning concerning the intravenous use of haloperidol and the occurrence of QTP, Tdp and cardiac arrest. In 2010, this warning was also added to the Haloperidol labeling in Germany. Subsequently, this led to a very emotional debate of the benefit-risk ratio of intravenous haloperidol which is considered to be one of the few effective standard treatments for delirious intensive care patients. Here, we review in vitro and in vivo data and present an updated analysis of pharmacovigilance data and our results of a cohort study at an intensive care unit (ICU) at Universitätsklinikum Schleswig-Holstein (UKSH), Campus Kiel.

Review of in vitro studies

Haloperidol inhibits hERG (a potassium channel), hERG conducts the I\textsubscript{K} current which regulates cardiac action potentials and thus the QT interval. QTP is associated with Tdp.

Haloperidol inhibits several other ion channels, e.g. sodium and calcium channels ("multi-channel blocker"). Therefore, there is no correlation between isolated inhibition of hERG and the resulting APD\textsubscript{3} (action potential duration to 90% repolarisation).

→ Haloperidol does not significantly change the ADP in vitro, neither dose-dependent nor independent.

Review of in vivo studies

Standard dosages of haloperidol confer a very low risk of cardiotoxicity compared to other antipsychotics (cf. poster #229 at this congress and data of Hollesboer 2008 below).

Only one cohort study showed a greater risk of QTP in the intravenous-haloperidol-group (p<0.01):

<table>
<thead>
<tr>
<th>Cases of QTP with different routes of application (Dosages were not significantly different. Data from Ozeki 2010)</th>
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<tbody>
<tr>
<td>i.v.</td>
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<tr>
<td>No QTP</td>
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<td>QTP</td>
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Overdose of haloperidol did not cause QTP in a recent cohort study (Berling 2015).

→ Haloperidol confers a low risk for QTP/Tdp in vivo but this risk may be greater for intravenous application.

Updated analysis of pharmacovigilance data

Disproportionality Analysis (DPA) for the drugs name “haloperidol” and for at least one of the adverse events “electrocardiogram at corrected interval prolonged” or “electrocardiogram QT prolonged” or “electrocardiogram QT interval abnormal” or “electrocardiogram T wave abnormal" (hereafter summarized as “QTP”); a second analysis for at least one of the adverse events “arrhythmia”, “torsade de pointes”, “ventricular arrhythmia”, “ventricular tachycardia” (hereafter summarized as “Tdp”)

→ Intravenous haloperidol is associated with a higher risk for cardiotoxicity (p<0.01). This confirms the FDA findings from 2007.

Efficacy and safety of haloperidol in a cohort study at an ICU

Methods: The data of 7158 patients of an anesthesia intensive care unit were collected between 2006 and 2012 and analyzed using propensity score matching to describe the actual dimension of the assumedly increased cardiovascular risk of intravenous haloperidol.

Results: Haloperidol was administered to 6.72% of the 7158 patients of the ICU. No QTP or Tdp was reported in the haloperidol-group. It was applied intravenously to 81.08%, via intravenous drip to 5.2% and orally to 13.72% of the haloperidol-patients. The ratio of male vs. female patients on the ward was 1.59, within patients receiving haloperidol 4.26, and within patients getting intravenous haloperidol 4.23. The cumulative haloperidol dosage did not correlate with decrease (r=0.023).

Therefore, propensity score matching taking in account length of stay (dichotomized for ≤5 days versus >5 days), age, sex, heart rate, systolic and diastolic blood pressure, ventilation mode, arterial oxygen saturation and the scales Simplified Acute Physiology Score (SAPS) and Therapeutic Intervention Scoring System (TISS) was employed. Data was available for 20.5% of all patients, so 169 haloperidol cases were matched 1:2 to 358 control cases. So, unlike in the cohort study and the pharmacovigilance analysis presented above, the severity of illness was taken into account here by propensity score matching, eliminating concerns that intravenous haloperidol is particularly used for more severe II II.

Unfortunately, the chance of survival was 2.9-fold higher for patients with intravenously injected haloperidol compared to patients without haloperidol, with a confidence interval of 1.8 - 4.8 and p<0.001.

→ Haloperidol was not associated with QTP/Tdp. Survival for patients receiving haloperidol was 2.9-fold higher.

Conclusions

Treatment of haloperidol for ICU patients when used was properly indicated by label and/or guidelines increases survival by 2.9-fold.

Intravenous haloperidol is associated with an elevated risk of cardiotoxicity in some cohort studies and pharmacovigilance analyses. This risk cannot be explained or reproduced in vitro. To avoid cardiotoxicity, we propose to reduce other risk factors, e.g., hypokalemia, hypomagnesemia, bradycardia or concomitant use of other QT-prolonging drugs and to carefully monitor the patient if other risk factors like female sex or old age or pre-existing abnormal ECG features such as long-QT-syndrome or abnormal T- or U-wave exist.

We consider haloperidol a safe and effective drug when proper precautions are taken.