Extended Abstract

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Pharmacology 2019: Is haloperidol safe in the presence of other QT prolonging drugs in the intensive care unit? - J. McLuckie - Glasgow Royal Infirmary

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Background and Aims:

ICU delirium is a common neuropsychiatric disorder, characterised by an acute fluctuation in consciousness. Haloperidol is used routinely in ICUs to both treat and prevent delirium, which strikes up to half of ICU patients and is associated with prolonged mechanical ventilation, longer ICU and hospital stays, and increased mortality. Haloperidol, the major tranquilizer par excellence, was synthesized 60 years ago in February 1958. Since then it has been used in hundreds of thousands of patients with schizophrenia and other psychoses, particularly for the management of psychosis-induced agitation, and is included in the World Health Organisation's list of essential medicines.

In 1974–1975, Seeman, by using a preparation of rat brain striatum, discovered that haloperidol selectively blocked the D2 dopamine receptors .This research laid the foundations of the dopamine hypothesis of schizophrenia, according to which meso-cortico-limbic dopamine pathways overactivation has a central role in this disease. This hypothesis also provides a biological basis to explain the observed efficacy of haloperidol not only in schizophrenia but also in delirium. Dopamine excess may cause some of the neurobehavioral alterations observed in patients with hyperactive or mixed type delirium, namely agitation, restlessness, irritability, increased psychomotor activity, distractibility, hyper alertness, combativeness, and psychotic distressing symptoms. This explains why dopaminergic drugs, such as the levodopa, can precipitate delirium, while dopamine antagonists like haloperidol and other antipsychotics can effectively control the behavioural signs of delirium. Dopamine D2 antagonists enhance acetylcholine release, which may be another mechanism by which these drugs help to alleviate the symptoms of delirium. Based on this multiplicity of effects, some experts suggest that haloperidol and other antipsychotic agents may be effective not only in the management of behavioural symptoms of delirium (agitation), but they might also be useful in patients with hypoactive delirium to control distressing psychotic symptoms such as hallucinations and delusions

In animals, dopamine agonists cause slowing of EEG despite motor hyperactivity, which matches the features of hyperactive delirium. More recent research has shown that D2 dopamine receptors in the cortex are a common target for both typical (haloperidol) and atypical antipsychotics, but these latter induce a significantly lower D2 binding than haloperidol in the basal ganglia, particularly in the striatum. This fits well with the association of antipsychotic efficacy (attributed to an anti-dopaminergic effect on the meso-cortico-limbic dopamine pathways) and lower extra-pyramidal side effects (attributed to anti-dopaminergic effect in the striatum) in atypical antipsychotics than with haloperidol. Study in human volunteers has confirmed that acute administration of haloperidol causes a state of impaired, though rapidly reversible, motor ability coinciding with diminished grey matter volume and connectivity in the striatum, a brain region that mediates movement. Results of past studies have been mixed, with some showing a benefit for haloperidol in the ICU and others not. Haloperidol is the main pharmacological agent used in the management. However, the European Medicines Agency recently suggested that Haloperidol is now contraindicated for utilisation in combination with other QT prolonging drugs due to the risk of ventricular tachyarrhythmia. Before practice changes to another potentially harmful alternative, it is essential to understand the influence of Haloperidol in combination with other QT prolonging drugs on VT in comparison to Haloperidol alone. It is necessary to correct for the influence of other factors including age, gender, electrolyte disturbances and a past medical history of Ischaemic Heart Disease or previous arrhythmia on VT. To ascertain if episodes of VT are clinically significant, it is important to determine the odds of VT requiring intervention in relation to each factor. The risk of QTc prolongation often raises concerns, although the effect of haloperidol on QTc interval has not yet been investigated during a randomised placebo-controlled fixed-dose study. QTc duration during haloperidol use changes differentially, increasing in patients with normal before-haloperidol QTc duration, but decreasing in patients with prolonged before-haloperidol QTc duration. Shorter before-haloperidol QTc duration and surgery before haloperidol use predict potentially dangerous QTc prolongation. Combined Use of HALDOL and Lithium An encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness

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and confusion, extrapyramidal symptoms, leukocytosis, elevated serum enzymes, BUN, and fasting blood sugar) followed by irreversible brain damage has occurred during a few patients treated with lithium plus HALDOL. A causal relationship between these events and therefore the concomitant administration of lithium and HALDOL has not been established; however, patients receiving such combined therapy should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear.

Methods: A case control study involving 4,189 admissions was performed. Electronic records for each were interrogated to provide information pertaining to the aforementioned factors and receipt use of QT prolonging drugs including Haloperidol. It was also documented as to whether the patient experienced VT during their stay. Multivariate regression analysis calculated odds ratios to ascertain factors associated with VT and to determine if these episodes were clinically significant, odds ratios were calculated for VT requiring treatment.

Results: Our results identified that 2.1% of ICU patients developed VT and that hypocalcaemia, IHD, previous arrhythmia and the administration of QT prolonging drugs were all associated with VT. The effect was strongest for Haloperidol administration without another QT prolonging drug (OR 12.309, 95% CI 3.396 – 44.618). The administration of a QT prolonging agent in combination with Haloperidol did not further increase this (OR 8.599, 95% CI 3.175 – 23.291). Intervention was required for 48.3% of patients that developed VT and included electrolyte replacement, antiarrhythmic drugs and DCCV. The administration of any QT prolonging drug resulted in the greatest odds of VT requiring treatment (OR 4.373, 95% CI: 1.337 – 14.299).

Conclusions: Despite concerns regarding its safety, Haloperidol should remain the first line treatment option in delirium since the chance of developing VT remains low, even though the odds are significantly increased. Additional QT prolonging drugs do not increase this further and this combination in patients whom it is clinically appropriate appears to be safe. However, alternatives including atypical antipsychotics should be considered in patients with concomitant risk factors such as IHD and previous arrhythmias.

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