5-HT$_3$ Antagonists (Antiemetics) & Cardiac Safety

Summary

Ondansetron is a highly effective antiemetic for the treatment of nausea and vomiting. However, this medication has also been associated with QT prolongation, which can result in serious cardiac harm. Pharmacogenomic studies on therapeutic response to ondansetron have been conducted, but no investigation has been performed on genetic factors that influence cardiac safety. Given that ondansetron is also used off-label, it is important to examine the cardiac safety of ondansetron, and the effect of genetic variation on effectiveness and safety in patients treated with ondansetron.

Implications

Patients who are at risk of developing ondansetron-induced QT-prolongation due to the presence of genetic variants, or the use of concomitant medications that alter CYP2D6 enzyme activity, can be identified before the treatment begins. This study has provided biologically-relevant findings beyond drug metabolism pathways. These findings represent the first step towards understanding and predicting this adverse event. Ultimately, these data will enable clinicians, patients, and their families to better evaluate the cardiovascular health risks and incorporate pre-emptive protective measures to minimize drug-induced harm while optimizing the likelihood of maintaining antiemetic effect of ondansetron.

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What is the current situation?

- Ondansetron, a 5-HT3 antagonist approved in Canada as an antiemetic, is used for the prevention of postoperative- and chemotherapy-related nausea and vomiting.
- Ondansetron is also used off-label to treat nausea and vomiting of pregnancy and hyperemesis gravidarum, and in the perioperative period during caesarean section.
- Ondansetron carries a warning on its product monograph regarding QT prolongation, which can result in serious cardiac outcomes.
- Genetic variants in CYP2D6, one of the major enzymes involved in the metabolism of ondansetron, have been associated with ondansetron-related effectiveness, with increased CYP2D6 enzyme activity resulting in lower ondansetron levels.
- No investigation has been performed on genetic factors that influence the cardiac safety of ondansetron.
- This highlights the need for active surveillance in Canadians treated with this medication in order to understand and address the current evidence gap.

What was the aim of the study?

- To prospectively determine and compare the cardiac safety profile of ondansetron in three groups – post-surgical children, pediatric oncology patients and pregnant women.
- To identify genetic variants associated with 5-HT$_3$ antagonist-induced QT prolongation.

How was the study conducted?

- Patients receiving ondansetron were enrolled from across Canada using the CIHR DSEN SEARCH & PREVENT adverse drug reaction surveillance network.
- 261 patients were recruited from clinics in three provinces: BC Children's Hospital, BC Women's Hospital & Health Centre Vancouver (Vancouver, BC), the Winnipeg Health Sciences Centre (Winnipeg, MB), and St. Michael's Hospital (Toronto, ON).
- A 12-lead ECG was recorded for each patient at 5 and 30 minutes after the first dose of ondansetron.
- Patient DNA samples were genotyped for approximately 5 million genetic variants across the genome, including candidate variants that have previously been associated with ondansetron treatment outcomes or QT prolongation.
- Genome-wide association analyses were performed to uncover genes involved in QT prolongation.

What did the study find?

- Ondansetron led to 24.1% of the patients developing prolonged QT intervals and 1.2% of patients exhibiting unsafe QT prolongation.
- The greatest shift in QT interval occurred at five minutes post-ondansetron administration, with the most significant shift observed in the pediatric surgery cohort (P=2.9 x 10^{-5}).
- Targeted analyses performed on *CYP2D6* did not detect any associations between *CYP2D6* activity score and ondansetron-induced QT prolongation (P=0.77) or the percentage change in QTc at 5-min post ondansetron administration (P=0.81).
- The absence of associations between candidate genetic variants and ondansetron-induced QT prolongation highlights the importance of using unbiased approaches to uncover biological insights for future investigation.
- This study discovered a novel variant in the *SLC36A1* gene that confers **25-fold lower risk** of QT prolongation (P=1.97x10^{-7}). *SLC36A1* transports a broad range of amino acid-based drugs and derivatives, including ondansetron. The *SLC36A1* genetic variant likely reduces the transport and absorption of ondansetron, leading to decreasing the risk of cardiac harm.
- A novel *TLR3* gene variant also identified in this study significantly **reduces** QT interval and **decreases the risk** of ondansetron-induced QT prolongation (P=2.00 x 10^{-7}). This gene variant likely increases the concentration of serotonin, which has been shown to shorten the QT interval.
- These important findings significantly advance the understanding of this potentially life-threatening adverse event, and provide an important first step towards improving the safety of this commonly used antiemetic medication.

Drögemöller BI, Wright GEB, Trueman J, Shaw K, Staub M, Chaudhry S, Miao F, Higginson M, Groeneweg G, Brown J, Magee LA, Whyte SD, West N, Brodie SM, 't Jong G, Israels S, Berger H, Ito S, Rassekh SR, Sanatani S, Ross CJD, Carleton BC. A pharmacogenomic investigation of the cardiac safety profile of ondansetron in children and pregnant women. Biomedicine & Pharmacotherapy 2022 April,148:112684. PMID: 35149390

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