Risk of Ventricular Arrhythmias and Association with Ondansetron

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Objectives To evaluate the use of ondansetron in a tertiary care pediatric health system, assess the incidence of ventricular tachyarrhythmia within 24 hours of ondansetron, and identify the characteristics of children experiencing a ventricular tachyarrhythmia after ondansetron, to identify potential risk factors.

Study design This retrospective chart review identified children ≤18 years of age who received ondansetron within 24 hours prior to a ventricular tachyarrhythmia. Those identified were evaluated for other diagnoses, concomitant medication use, electrolyte abnormalities, or underlying conduction abnormalities that may have contributed to the arrhythmia.

Results A total of 199 773 doses of ondansetron were administered to 37 794 patients over 58 009 visits. Average dose was 0.13 mg/kg/dose (range 0.005-0.86 mg/kg/dose). Seven patients received ondansetron within 24 hours prior to a ventricular arrhythmia. All 7 patients had underlying congenital cardiac conduction abnormalities (n = 3) or other major cardiac diagnoses (n = 4). In clinical review, torsades de pointes was found in only 1 of the 7 patients.

Conclusions This retrospective study found the risk of ventricular arrhythmia within 24 hours after ondansetron administration was 3 in 100 000 patients treated annually (0.003%). Children with major cardiac conditions could be considered for electrocardiogram screening and continuous cardiac monitoring while receiving ondansetron. Our findings do not support recommendations for electrocardiogram screening or continuous monitoring of other pediatric populations receiving ondansetron. *(J Pediatr 2016;179:118-23).*

In 2011, regulatory bodies, including the US Food and Drug Administration (FDA), issued precautionary statements concerning the safety of ondansetron.[1-3] This precaution is based largely on QT prolongation demonstrated in animal models, in addition to limited human data showing an effect on the QT interval. Similar warnings have been issued by Britain's Medicines and Healthcare products Regulatory Agency, Health Canada, and the Australian Therapeutic Goods Administration.[4-6] In 2012, both the US FDA and Britain's Medicines and Healthcare Products Regulatory Agency issued communications to healthcare professionals stating that no single dose of ondansetron should exceed 16 mg because of the risk of QT prolongation.[2,4] Similar restrictions are being placed elsewhere, worldwide.

Even though US FDA Safety Communications state, "Torsades de Pointes, an abnormal, potentially fatal, heart rhythm, has been reported in some patients receiving ondansetron," to date, the published regulatory statements or warnings do not demonstrate an association between ondansetron and tachydysrhythmia.[1] There are a few pediatric case reports that associate ondansetron with onset of ventricular tachycardia or polymorphic ventricular tachycardia.[7-10] A small retrospective cohort study of children with congenital long QT syndrome (LQTS) suggested an increased risk of arrhythmias after ondansetron administration.[11] Most pediatric reports of ondansetron use and off-target cardiac effects were largely confined to perioperative or oncology patients.[11-13] A recently published comprehensive review described 60 unique arrhythmia reports (11 pediatric and 49 adult) within 24 hours of ondansetron administration and found no reports of arrhythmia were associated with a single oral ondansetron dose.[14] The large-scale use of this medication for pediatric patients highlights the importance of evaluating its safety more broadly in children.[15-17] The objectives of this study were to evaluate the use of ondansetron in a tertiary care pediatric health system, assess the incidence of ventricular arrhythmia within 24 hours of ondansetron, and identify the characteristics of children experiencing a ventricular arrhythmia after ondansetron so as to identify potential risk factors for pediatric patients.

Methods

This was a retrospective cohort study of children 18 years of age or younger who received ondansetron at Children's Hospital of Wisconsin or outpatient clinics at

BMT	Bone marrow transplant
ECGs	Electrocardiograms
FDA	Food and Drug Administration
ICD-9	*International Classification of Disease, Ninth Revision*
LQTS	Long QT syndrome
TdP	Torsades de Pointes
VT	Ventricular tachycardia

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the Milwaukee Campus (**Figure 1**; available at www.jpeds.com) between January 1, 2006, and December 31, 2011. No guidelines for monitoring or use of ondansetron were in place in this health system during that timeframe. Prescribing practices for ondansetron likely changed following the US FDA safety communication, therefore, patient enrollment concluded on December 31, 2011. This study was approved by the Children's Hospital of Wisconsin's Investigational Review Board.

Patients included in the study population received ondansetron and were subsequently either discharged with (1) an *International Classification of Disease, Ninth Revision* (ICD-9) discharge code 427.1 (for Torsades de Pointes [TdP], ventricular tachycardia [VT], or paroxysmal ventricular tachycardia), 427.2 (paroxysmal tachycardia unspecified), 427.4 (ventricular fibrillation and flutter), 427.41 (ventricular fibrillation), 427.42 (ventricular flutter), 427.5 (cardiac arrest), 427.89 (other specified cardiac dysrhythmias), 427.9 (other unspecified cardiac dysrhythmias); or (2) had a signal event during the encounter. A signal event was defined as an in-hospital death or a medical emergency that resulted in entry into the Children's Hospital of Wisconsin Code Database with a rhythm of VT, TdP, or rhythm not otherwise identified. Extensive chart review identified the date(s) and time(s) of the ondansetron administration relative to the onset of the ventricular arrhythmia(s). Patients were included in the case review if ondansetron was administered within the 24-hour period before the occurrence of ventricular arrhythmia. Twenty-four hours was chosen based on the pharmacokinetics of ondansetron and the expected absence of therapeutic levels after 24 hours.

The medical records for these patients were reviewed by a pediatric cardiologist, a medical toxicologist, a pediatric emergency medicine physician, and a pharmacist for the following information: other diagnoses, ondansetron dose, concomitant medications, and laboratory data to determine presence or absence of electrolyte abnormalities. Concomitant medications were evaluated for their potential to cause QT prolongation or TdP as identified in the CredibleMeds QT Drugs Lists (formerly the Arizona Center for Education and Research on Therapeutics) web resource for medications with risk of TdP or possible risk of TdP.[18,19] Available electrocardiograms (ECGs) in the timeframe around the event were reviewed to determine if the patient had documented QT prolongation. Rhythm strips during the event were reviewed to identify the specific dysrhythmia.

Descriptive statistics were utilized for analyses. The number of doses and proportion of children administered ondansetron was reported for the entire cohort and subgroups of children evaluated in the emergency department and on the oncology and bone marrow transplant (BMT) services. The incidence of ventricular arrhythmias after ondansetron was a proportion calculated for these same groups during the 6-year study period. Characteristics of children were described and tabulated.

Results

During the study period, there were 1 687 894 patient visits during which ondansetron was administered at 58 009 (3.4%) patient visits (**Figure 1**). This includes 199 773 doses of ondansetron administered to 37 794 patients distributed across all ages (**Figures 1** and **2**). Emergency department and outpatients accounted for 27 297 patient visits (47%) of all patients who received ondansetron and 41 901 (21%) of the total doses administered. The average single dose of ondansetron administered in the emergency department was 4.9 mg (median: 4 mg; range 0.11-36 mg) or 0.13 mg/kg/dose (median: 0.1 mg/kg/dose; range 0.005-0.86 mg/kg/dose). Oncology and BMT patients accounted for 1.9% (733 patients) of all patients who received ondansetron and 43.1% (86 007 of the 199 773 doses) of the total doses administered. The average single dose of ondansetron administered to oncology/BMT patients was 5.2 mg (median: 4 mg; range 0.11-36 mg) or 0.14 mg/kg/dose (median: 0.12 mg/kg/dose; range 0.005-0.74 mg/kg/dose). Patients receiving chemotherapy received higher single

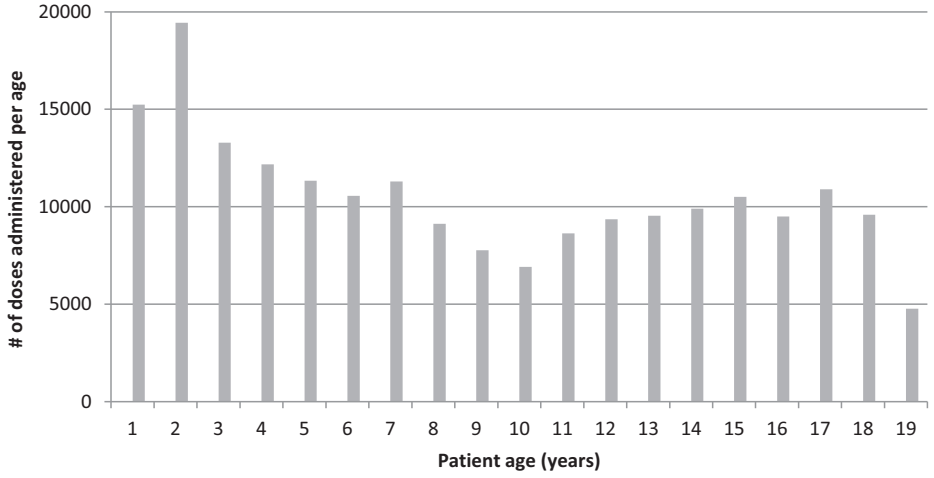

Figure 2. Ondansetron doses administered by patient age.