Drug Safety Evaluation

Cardiac safety concerns for ondansetron, an antiemetic commonly used for nausea linked to cancer treatment and following anaesthesia

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Word number =

1. Introduction

2. Non-cardiac pharmacology

3. Pre-clinical data on cardiac electrophysiology

4. Human heat rate

5. Human heart QT interval

6. Ischemia and arrhythmias

7. Expert opinion
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Abstract

Introduction: Ondansetron is a 5-HT₃ receptor antagonist commonly used as an anti-emetic to prevent the nausea and vomiting associated with anti-cancer drugs, cancer radiotherapy, or postoperatively. Recently, the US Food and Drug Administration (FDA) issued a warning for ondansetron due to a potential for prolongation of the QT interval of the electrocardiogram (ECG), a phenomenon that is associated with an increased risk of the potentially fatal arrhythmia torsade de pointes.

Areas covered: We undertook a review of the cardiac safety of ondansetron. Our primary sources of information were PubMed (with downloading of full articles), and the internet.

Expert opinion: The dose of ondansetron that the FDA has concerns about is 32 mg iv (or several doses that are equivalent to this), which is only used in preventing nausea and vomiting associated with cancer chemotherapy. This suggests that ondansetron may be safe in the lower doses used to prevent the nausea and vomiting in radiation treatment or postoperatively. However, as there is a report that a lower dose of ondansetron prolonged the QT interval in healthy volunteers, this needs to be clarified by the FDA. More research needs to be undertaken of the relationship between QT prolongation and torsades in order that the FDA can produce clear-cut evidence of pro-arrhythmic risk when introducing warnings for this.

Key words cardiac safety, FDA, ondansetron, proarrhythmia, QT interval, torsades de pointes
1. Introduction

Nausea and vomiting are common complications of cancer chemotherapy and can also occur following anaesthesia. Prior to the development of ondansetron, the emesis caused by anti-cancer drugs, cancer radiotherapy, or postoperatively was difficult to prevent [1]. Ondansetron is a member of the serotonin (5-HT₃) receptor antagonist drug class, and this class of drug is good at preventing this nausea and vomiting [2,3].

Ondansetron was granted FDA approval in 1991, and has been widely used, often in combination with other antiemetic agents (dexamethasone, aprepitant), and often for the prevention of vomiting and nausea caused by high-emetic-risk chemotherapy [4]. However, in late 2011 the US FDA released a Safety Communication indicating an ongoing safety review of ondansetron due to a potential for prolongation of the QT interval of the electrocardiogram (ECG), a phenomenon that is associated with an increased risk of the potentially fatal arrhythmia torsade de pointes [5]. In addition, the manufacturer of ondansetron, Zofran, (GlaxoSmithKline) was required to conduct a “thorough QT” study to establish the extent to which ondansetron could induce QT interval prolongation [5]. On the 12th April, 2012, the FDA notified health care professionals that the 32 mg, single intravenous dose of ondansetron would no longer be marketed because of the potential for serious cardiac events [6]. At the end of June 2012, a third FDA Safety Communication was released: preliminary analysis of the thorough QT study data suggested that intravenous ondansetron produces concentration-dependent prolongation of the rate-corrected QT (QTc) interval, with a marked prolongation of the QTc interval at the highest tested dose [7]. An independent database of drugs with a risk of QT prolongation/torsades de pointes (AZCert.Org) currently lists ondansetron amongst drugs that “cause QT prolongation but there is insufficient evidence that they, when used as directed in labeling, have a risk of causing TdP” [8].

As a result of these FDA warning about ondansetron, we decided to undertake a review of the cardiac safety of ondansetron. As several aspects of the non-cardiac pharmacology of ondansetron may affect its clinical cardiac safety, we start by briefly considering the pharmacology with emphasis on factors that may influence its cardiac safety (e.g. plasma levels). Then, we consider both the preclinical and clinical effects of ondansetron on cardiac electrophysiology with particular emphasis on changes in ventricular repolarisation, as these may underlie the effects on the QT interval. Finally, we provide an expert opinion which includes attempting to provide both insight into the underlying
mechanisms of ECG alterations seen in humans with ondansetron and a context in which to view the recent safety concerns voiced by the FDA [5,6,7].

2. Non-cardiac pharmacology

2.1 Pharmacodynamics

Ondansetron \(((RS)-9\text{-methyl}-3-[(2\text{-methyl}-1H\text{-imidazol}-1\text{-yl})\text{methyl}]\text{-2,3-dihydro-1H-carbazol-4(9H)-one})\) was one of the first drugs developed as a selective 5-HT₃ receptor antagonist [9]. It is widely considered that ondansetron exerts its antiemetic effects in subjects being given highly emetic anticancer drugs, by acting as an antagonist at 5-HT₃ receptors both centrally in the chemotrigger zone and nucleus tractus solitaries, and peripherally by inhibiting 5-HT binding to vagal afferents in the gastrointestinal tract [10]. The following sections have evidence that higher doses of ondansetron are required to be effective in preventing nausea and vomiting in cancer chemotherapy than the doses required for prophylaxis in radiation treatment or postoperatively.

2.2 Cancer chemotherapy

There is some evidence to support a dose-antiemetic relationship with ondansetron. Thus, during multiple dosing with intravenous ondansetron (0.01 to 0.48 mg/kg) of 28 subjects receiving the chemotherapeutic agent cisplatin, a correlation between anti-emetic efficacy and AUC ondansetron has been suggested [11]. In this study, the trough levels of ondansetron ranged from ~50-200 ng/ml, 0.25-0.55 µM [11]. In another study, when a high dose of ondansetron (0.18 mg/kg iv) was compared with a low dose (0.01 mg/kg iv) in subjects taking high-dose cisplatin, less emesis and nausea was observed with the high dose, and both doses were well tolerated [12]. When ondansetron 0.15 mg/kg iv every 4 hours x 3, was compared with ondansetron 32 mg iv or ondansetron 8 mg iv, in subjects being given anticancer emetic cisplatin, the subjects given ondansetron 32 mg had a better outcome (less nausea and more food intake) than with ondansetron 8 mg or the standard dose of ondansetron 0.15 mg/kg [13]. A study comparing ondansetron 32 mg versus ondansetron 8 mg every 6 hours x 4 in subjects being given cisplatin, also showed a better antiemetic profile with the 32 mg than 8 mg [14].

With oral ondansetron, 8 mg twice daily was similar effective to 8 mg three times daily in preventing emetic episodes in ~60% of 402 subjects taking the moderately emetogenic anticancer drug cyclophosphamide [15]. Also, there were no differences in the appetite ratings and nausea scores, or adverse effects between ondansetron twice or three times daily [15].
Ondansetron is also used in combination with dexamethasone to prevent emesis with chemotherapy. The rate of complete responses (no emetic episodes) was similar in subjects given dexamethasone and ondansetron 8, 24 or 32 mg intravenous, suggesting that the maximum effect could be achieved with the lowest dose of ondansetron [16]. However, even with the combination, only about half of the subjects had no nausea [16]. Ondansetron 32 mg iv has also be used in combination and dexamethasone and the neurokinin-1 antagonist, aprepitant, as the addition of aprepitant further reduced the nausea and vomiting in subjects who received cisplatin-based chemotherapy [17].

The most recent consensus recommendations for the prevention of vomiting and nausea following high-emetic–risk chemotherapy suggests that ondansetron is one of 5 possible 5-HT3 receptor antagonists to be used, and that the oral dose of ondansetron should be 24 mg and the intravenous dose 8 mg or 0.15 mg/kg, and that the antagonists should be used in combination with dexamethasone and aprepitant [4].

### 2.3 Prophylaxis of radiation nausea and vomiting

In 111 subjects undergoing fractionated radiotherapy, ondansetron 8 mg bid first day of treatment through to 2 days after treatment was compared to placebo, and shown to be effective in 67% of subjects, compared to 45% with placebo [18]. With a loading dose of ondansetron of 8 mg before radiation therapy, and 8 mg bid for 3 days after the radiation therapy, ondansetron gave complete or major control of emesis in 94% of subjects, which was much better than the ~40% control with the combination of chlorpromazine and dexamethasone [19].

### 2.4 Post-operatively

*Meta-analysis, of the trials of ondansetron for the prophylaxis of postoperative vomiting in 12,078 subjects, showed that a 4 mg dose of ondansetron prevented this vomiting in one of 6 subjects, with three not vomiting regardless of treatment, and two vomiting despite treatment [20]. A subsequent trial in subjects at high risk of postoperative nausea and vomiting showed that ondansetron reduced the risk of this by ~25% [21].*

### 2.5 Pharmacokinetics

In determining whether the effects of a drug observed experimentally are likely to occur clinically, it is important to determine the plasma levels of drugs in humans, and relate the levels used experimentally to those used clinically to determine if the experimental findings are likely to be clinically relevant. After a single intravenous dose of ondansetron 0.15 mg/kg intravenously, the
peak maximum concentration in 30 healthy volunteers was 104 ng/ml (0.28 µM), the AUC was 359 ng/h/ml and the half-life was 3.8 h [22].

More recently, it has been reported that after a single intravenous dose of ondansetron 32 mg in healthy subjects, there was a peak concentration of ~408 ng/mL (1.11 µM), and the total area under the plasma-time curve of 1268.3 ng.h/mL [23]. The levels of ondansetron were not altered by the neurokinin-1 receptor antagonist aprepitant, which is used in combination with ondansetron and dexamethasone to prevent chemotherapy-induced nausea and vomiting [23].

After the effectiveness of intravenous ondansetron as an anti-emetic was established, ondansetron was developed for oral administration. After oral and intravenous administration of ondansetron 8 mg, the maximum plasma concentrations and AUC are higher after intravenous administration, and higher in the elderly than young (maximum plasma levels: iv; 83 ng/ml, ~ 0.23 µM, in young and 114 ng/ml, ~0.31 µM, in old; oral 26 ng/ml, ~0.07 µM, vs 31 ng/ml, ~0.08 µM in old) [24].

After the oral administration of ondansetron 8 mg to 20 subjects with cancer, the bioavailability is ~85%, indicating good absorption from the gastrointestinal tract, and limited first pass metabolism [25]. The peak maximum plasma concentration of ondansetron was 381 ng/ml (1.04 µM), and AUC (381 ng.h/ml) [25], but both of these values had high variation.

The primary route of ondansetron clearance is liver metabolism, with less than 5% of an iv dose excreted unchanged in the kidney [26]. The clearance of ondansetron decreases significantly with age being 0.38, 0.32 and 0.26 L/h/kg in young (18-40 years), elderly (60-74) and very aged people (>75 years), respectively [22]. The major metabolite, 8-hydroxyondansetron, is equivalent in potency as a 5-HT3-receptor antagonist to its parent [22]. As a consequence of liver metabolism, the pharmacokinetics of ondansetron are altered by impaired liver function. Thus, after a single intravenous dose of ondansetron 8 mg the peak concentration was 97 ng/ml (0.27 µM) in healthy volunteers, and although this was not altered by hepatic impairment, the AUC (ng.h/ml) of 279 was progressively increased in mild, moderate and severe hepatic dysfunction [27]. In severe cirrhosis of the liver, the clearance is slowed and the half-life extended to 15-20 hours, and thus a maximum dose of ondansetron 8 mg total/day is recommended in severe hepatic dysfunction [22].

There is evidence that the S(+) and R(-)-isomers are metabolised in different ways, and are therefore subject to different genetic effects. Thus, in subjects given ondansetron 4 mg, prior to general anaesthesia, with high (ultrarapid) and no CYP2D6 activity, there are different AUC values of the S(+) ondansetron enantiomer of ~150 ng.h/ml and 363 ng.h/ml, respectively [28]. After ondansetron 8 mg, the AUC values were ~154 and 437 mg.h/ml for S(+) -ondansetron in high and no CYP2D6
activity, respectively [28]. After the administration of ondansetron 8 mg, but not 4 mg, CYP3A expressor status selectively altered R-ondansetron AUC with low and high status giving AUCs of 383 and 138 mg.h/ml, respectively [28]. In contrast, there was no association between the AUC of R(·)-ondansetron and CYP2D6 activity or between the AUC of S(+)-ondansetron and CYP3A activity [28].

Ondansetron is typically administered in tablet or liquid form or intravenously, prior to commencement of chemotherapy, radiotherapy, surgery or emergence from anaesthesia. It can be taken orally throughout chemotherapy/radiotherapy, with subsequent discontinuation - sometimes with a delay - following the end of treatment.

3. Pre-clinical data on cardiac electrophysiology

From the previous section, the peak concentrations of ondansetron observed in humans are about 1 µM. In 1991, ondansetron at 1.31 mg/kg iv was reported to have no effect, and at higher doses, 2.63 and 5.25 mg/kg iv, to prolong the QT interval of anaesthetised dogs by 19 and 28% (~60 and 90 msec), respectively, without having any effect on the other ECG parameters or blood pressure and heart rate [29]. Subsequently, de Lorenzi and colleagues showed that on feline ventricular myocytes, and at 1 µM, ondansetron prolonged ventricular APD₉₀ by ~46% (at a stimulation frequency of 0.5 Hz), and that the effect of ondansetron was readily reversible on drug washout [30]. The effects of ondansetron on APD₉₀ were found to exhibit reverse rate dependence (being abolished at a stimulation frequency of 3Hz) [30]. Using voltage-clamp experiments on feline ventricular myocytes, they showed that ondansetron inhibited delayed rectifier K⁺ current, Iₖ, with an observed Kₐ of 1.7 ± 1.0 µM [30]. The voltage-dependent activation profile of the current affected by the two drugs is consistent with a primary identity as the rapid delayed rectifier K⁺ current, Iₖr [30]. Ondansetron produced a modest left-ward shift in voltage-dependent activation of the current and slowed deactivation of Iₖ tails, producing a ‘cross-over’ phenomenon, features consistent with preferential drug interactions with channels in the open (activated) state. The inhibition with ondansetron was not strongly voltage-dependent.

In 2000, Kuryshev et al showed that ondansetron was a weak inhibitor of cloned human Na channels (IC₅₀ of 88.5 µM) [31]. The characteristics of the observed I₉₅ block were consistent with a preferential interaction with Na channels in the inactivated state [31]. These authors also tested the effects of ondansetron on recombinant channels encoded by hERG (human ether-à-go-go-related gene, alternative nomenclature KCNH2), which pass current similar to native cardiac Iₖr [32,33]. Kuryshev et al showed that ondansetron inhibited hERG K⁺ channel current (IₒERG) with an IC₅₀ of 0.81 µM [31]. Ondansetron also produced an apparent slowing of IₒERG deactivation, consistent with the
earlier findings on native $I_k$ by de Lorenzi et al (1994) and with a preferential interaction between the drug and hERG channels in the open state. Ondansetron at 10 µM was only a weak inhibition of KvLQT1+minK (KCNQ1+KCNE1) channels responsible for cardiac $I_{ks}$.[31].

Two studies have used Purkinje fibres to explore APD modulation by ondansetron. Purkinje fibres offer a sensitive assay for drug-induced effects on AP repolarization, due to their weak repolarization reserve and consequent high sensitivity to $I_{Kr}$/hERG blocking drugs [34,35]. In one study of rabbit Purkinje fibres driven at 0.2 Hz at 0.1 µM, ondansetron prolonged APD$_{90}$ by 5.3% whilst at 10 µM a prolongation by 76% was observed [36]. The effect of ondansetron showed reverse use-dependence i.e. prolongation was smaller at higher frequencies [36]. The same study also assessed droperidol, which in addition to prolonging APD produced noticeable triangulation of AP morphology (this did not occur for ondansetron) [36]. Early after depolarizations (EADs), which are indicators of potential arrhythmia, occurred in 1 of 8 fibres treated with ondansetron at 1 µM, whereas 4 of 7 Purkinje fibres produced EADs with this concentration of droperidol and 6 of 7 at a higher concentration of 10 µM [36]. In a second study of rabbit Purkinje fibres driven at 1 Hz, ondansetron (1-10 µM) prolonged APD in a concentration-dependent fashion [37]. Application of the dihydropyridine L-type Ca channel inhibitor nifedipine abbreviated ondansetron-induced changes to APD [37].

4. Human heart rate

Ondansetron was approved for use by the FDA in 1991, and there are no publications on the clinical effects on the heart prior to this. In 1993, it was shown that the rapid infusion of ondansetron, 1, 4 and 8 mg, had no effect on heart rate, blood pressure, oxygen saturation or respiratory rate over a 5 minute period in 71 female subjects requiring anaesthesia prior to surgery [38]. In 1995, it was reported that the intravenous administration of ondansetron 0.15 mg/kg had no effect on heart rate or blood pressure in children, two-16 years old, prior to elective tonsillectomy [39].

5. Human QT interval

5.1. Adults

After intravenous administration of ondansetron, the highest concentration will occur immediately. In 1996, in 30 healthy male volunteers, ondansetron (32 mg/kg iv) statistically significantly increased the QT interval by 4.8 msec, and also produced a small increase in JT (6.4 msec), but had no significant effect on the QTc intervals, but did cause a slight decrease in heart rate (≤ 2 beats/min) [40]. In this study, effects were monitored from 15 minutes and changes were usually seen within 4 hours of drug administration and values returned to baseline within 8 hours [40]. Effects of ondansetron occurring in the first 15 minutes after infusion would not have been apparent with this
protocol. In a double-blind study of cancer patients the same year, ondansetron (32 mg i.v.) was found to produce “asymptomatic” ECG changes including QT and QTc prolongation by 5.9 and 6.3 msec after 1-2 hours [41]. Effects of ondansetron on the ECG at earlier time points are not reported in this study.

In a separate study of young healthy subjects, in the following year, after ondansetron 32 mg iv, one subject of 13 had an increase in systolic blood pressure from 113 to 163 mm Hg, and there was a QTc prolongation from a mean value of 385 to 390 msec, 5 msec, which was significant, whereas in the placebo group, the QTc interval increased from 377 to 383 msec, 6 msec, but this was not significant [44]. In this study, ondansetron had no effect on the PR or QRS interval [42]. A study of about 700 subjects with cancer in the same year showed that ondansetron (32 mg iv or 8 mg orally bid) prolonged QTc interval in 68 (19%) and QRS in 30 (9%) of the subjects [43]. No details of the degree of prolongation were given in this study.

A 2002 review of the cardiotoxic potential of 5-HT3 receptor antagonist antiemetics, including ondansetron, suggested that these agents were the best antiemetic option for subjects receiving emetogenic and cardiotoxic chemotherapy, as they had the fewest apparent cardiac effects [44].

In 2005, ondansetron was studied in 83 subjects being treated for post-operative nausea and vomiting in the recovery room, and 21% exhibited prolonged QTc intervals prior to drug administration (> 450 msec), possibly due to a perioperative increase, and ondansetron (4 mg i.v.) produced QTc prolongation, with maximal prolongation of 20 ± 13 msec at the third minute following ondansetron [45]. From their findings, Charbit et al suggested that the perioperative increase in QTc interval could be due to hypothermia, or to the anaesthetic, as propofol, thiopental, halogenated agents or opioids all interact with the potassium channels involved in repolarization [45]. In 2008, the same group shown that ondansetron 4 mg iv prolonged the QTc by 17 msec in healthy volunteers [46]. Thus, the magnitude of prolongation of QTc by ondansetron is similar in healthy volunteers or in postoperative subjects.

A separate recent randomized, placebo-controlled, double-blind study comparing differing doses of i.v. bolus ondansetron in 136 subjects who had surgical operations, showed there was significant and similar QTc prolongations with 4 or 8 mg of ondansetron (8 msec at 10 minutes), but no difference between placebo with 1 mg of ondansetron – which was nevertheless effective against post-operative nausea and vomiting [47]. Thus, the dosing regimen used may influence propensity towards any QTc prolongation.
A recent study has investigated effects of intravenous ondansetron 4 mg on the QT interval of 40 subjects hospitalized with cardiovascular disease (acute coronary syndromes or heart failure), with one or more other risk factors for torsades des pointes (hypomagnesaemia, hypokalaemia, congenital long QT syndrome, baseline QTc > 500 msec, female gender, old myocardial infarction, bradycardia, or receiving a drug that has a risk of causing TdP [48]. Thus 20 subjects were receiving either citalopram or ranolazine, 13 venlafaxine and 10 were receiving levofloxacin, erythromycin, or methadone [48]. A significant QTc prolongation by 19.3 ± 19 msec was found across the population studied when 120 minutes after the administration of ondansetron [48]. The QTc prolongation from ~443 msec by 18.3 ± SD = 20 msec and 20.6 ± 20 msec for acute coronary syndromes and heart failure, respectively [48]. Forty six percent and 31% subjects with acute coronary syndromes and heart failure, respectively, were considered to meet criteria for a prolonged QTc interval [48]. On the basis of these findings the authors recommended that patients who are at high risk for torsades who receive ondansetron should be monitored by telemetry [48].

In addition to ondansetron, another drug that is used to prevent emesis, droperidol, has been shown to prolong the QTc, which prompted the FDA issue to issue a black box warning about this drug [49]. Nevertheless, it has been suggested that ondansetron may be used with droperidol in preventing emesis, as having different mechanisms of anti-emesis, their effects may be additive, and this has been demonstrated in a clinical trial [50]. In 160 subjects undergoing laparoscopic surgery, there was a transient QTc prolongation with ondansetron 4 mg (10 msec after 5 min) and droperidol 1.25 mg (11 msec) when given separately, or in combination (13 msec), and the QTc had returned to baseline after 2-3 hours [50]. A second combination study, this time using 16 healthy volunteers, reported 17 ± 10 msec QTc interval prolongation with ondansetron 4 mg and 25 ± 8 msec QTc prolongation with droperidol 1 mg. In combination, the maximal change to QTc interval was 28 ± 10 msec, which was significantly longer than that produced by ondansetron alone, but not by droperidol alone [51].

5.2 Children and long QT syndrome

In 2005, a study in 22 children receiving chemotherapy for acute leukaemia, suggested that ondansetron 0.1 mg/kg had no effect on the ECG at 1, 3, 6 and 24 hours [52]. Similarly, in 2006 Pinarli et al reported no effect of ondansetron 0.15 mg/kg iv on the ECG in 40 children with cancer [53]. A recent study of 80 children receiving ondansetron (100 µg/kg), or droperidol (20 µg/kg) or both drugs, or saline for elective day-case surgery has noted 10-17 ms prolongation of QT interval with ondansetron and droperidol, but this was not significant as there were similar differences in the saline/placebo group [54]. This study also measured transmural dispersion of repolarisation (as the
interval between the peak and end of the T wave), as this may be a better predictor of torsades des points than QTc prolongation, and showed that ondansetron had no effect on this dispersion and no arrhythmias were seen [54]. Collectively, these results led the authors to conclude that these drugs are normally safe at the doses used [54].

Long QT syndrome (LQTS) is a disorder or cardiac ion channels resulting in prolongation of the QT interval. Subjects with congenital LQTS are susceptible to torsades de pointes, which may be drug-induced. This is exemplified by recent studies of children with previously undiagnosed or overt LQTS. Thus, a recent case report describes rapid onset of polymorphic premature ventricular contractions followed by polymorphic ventricular tachycardia after the administration of 0.1 mg/kg ondansetron and dimenhydrinate 4 mg/kg to an 11 year old girl undergoing surgery for cyst removal [55]. The girl showed a markedly prolonged QT interval of 590 msec, which reduced, but remained longer than usual values postoperatively [55]. The authors suggest that the prolongation was due to ondansetron, as the histamine H1-receptor antagonist dimenhydrinate had not previously been reported to prolong QTc, although other H1-receptor antagonists with similar structures have been [55]. The girl was subsequently diagnosed with congenital LQTS [55].

A separate study of 76 subjects with congenital LQTS, and a mean age of ~13 years, who received a total of 114 episodes of anaesthesia found a 2.6% incidence of adverse events/arrhythmias (3 subjects) [56]. All of the subjects were receiving β-adrenoceptor blocker pre-operatively, and the adverse effects occurred during emergence from anaesthesia in close proximity to receipt of both reversal (anticholinesterase/anticholinergic) drugs and ondansetron, and were not linked to the volatile anaesthetics used [56]. Nathan et al suggest that as the adverse effects occurred during the time of increased sympathetic activity, administration anticholinesterase/anticholinergic drugs, and ondansetron that a synergism of multiple factors contributed to the adverse event [56].

6. Ischemia and arrhythmia

In 1991, Ballard and colleagues reported seven cases of elderly patients in whom ondansetron administration produced chest pain, when being used to prevent emesis with chemotherapy [57]. Ballard et al pointed out that this was only an association, and that three of the subjects were taking anticancer drugs known to have cardiotoxicity [57]. In 2000, a second case report was published of acute myocardial ischaemia in a 60 year old woman who received ondansetron 2 mg iv after a lower lobectomy, who developed severe substernal chest pain [58]. On the ECG, she had ST segment depression and runs of ventricular tachycardia [58]. Again, there was no sign of myocardial damage or cardiac ischaemia after recovery [58]. In a female subject receiving cyclophosphamide for
systemic lupus erythematosus, ondansetron 4 mg iv caused constrictive chest pain and dyspnoea, and ischemic changes in the anterior ECG leads, which normalised over time [59].

Cases of supraventricular tachycardia and bradycardia have also been reported with ondansetron. In one case, a 34 year old man under anaesthesia was given metoclopramide 10 mg and then 20 minutes later ondansetron 2 mg iv, at which time he developed marked bradycardia (50 bpm) and then a junctional rhythm of <30 bpm [60]. It is unclear whether or not these changes are attributable to ondansetron, however, as metoclopramide has been associated with supraventricular tachycardia [61] and with bradyarrhythmias in one subject when co-administered with digoxin [62].

One case of fatal ventricular tachycardia associated with ondansetron use has been reported [63]. A 14 year old girl presenting with vomiting and abdominal pain received 4 mg ondansetron intramuscularly together with an antacid. Within 2-3 hours she developed tachycardia and circulatory failure; ventricular tachycardia degenerated into ventricular fibrillation, leading to death [63]. However, QT interval data were not reported and post-mortem analysis was not possible in this case [63].

There are also reports of atrial fibrillation with ondansetron. A 47-year-old female, who was having a benign breast lump removed, has also been reported to have atrial fibrillation after her second dose of ondansetron 4 mg [64]. In a 51-year-old male, who had elective surgery, after a second dose of ondansetron 4 mg iv caused nausea and diaphoresis, and his ECG showed atrial fibrillation and inferolateral ST segment elevation and ST segment alterans [65].

Symptomatic sinus bradycardia with ondansetron 4 mg has been reported in one female, undergoing laparoscopic cholecystectomy, who had no signs of cardiac problems when tested on recovery [66].

7. Expert opinion

7.1 Dose and safety of ondansetron

Higher doses of ondansetron seem to be required to be effective in preventing nausea and vomiting in cancer chemotherapy than the doses required for prophylaxis in radiation treatment or postoperatively. The dose of ondansetron that the FDA has concerns about is 32 mg iv (or several doses that are equivalent to this), which is only used in preventing nausea and vomiting associated with cancer chemotherapy. This suggests that ondansetron may be safe in the lower doses used to prevent the nausea and vomiting in radiation treatment or postoperatively.

7.2 Published literature and FDA findings
Our reading of the published literature has evidence that ondansetron prolongs the QTc interval, but there are no major studies specifically reporting torsade de pointes. However, the FDA has reported that torsades occurred in some subjects receiving ondansetron [7]. Although the FDA did not report which dose/s of ondansetron caused torsades, they suggest the use of a single 32 mg iv dose of ondansetron should be avoided, but that iv doses up to 16 mg and oral doses of 24 mg could still be used [7]. The published literature shows that ondansetron prolongs the QTc interval in conditions in which the interval is already prolonged, and the FDA confer that subjects who already have a prolonged QTc interval due to congenital LQTS, congestive heart failure or who are taking concomitant medication that prolong QT interval may be at particular risk [7]. The FDA also recommends not using ondansetron in subjects with bradycardias, and correcting electrolyte imbalances (e.g. hypokalaemia or hypomagnesaemia) prior to infusing ondansetron [7]. We suggest that it would be helpful for the FDA to make available any detailed information in its possession that ondansetron induces torsades.

7.3 QTc prolongation and the International Conference in Harmonization (ICH)

The testing of all new drugs for QTc interval prolongation is governed by two sets of ICH guidelines: ICH S7B for non-clinical evaluation [67] and ICH E14 for clinical evaluation [68]. The ICH S7B guidelines recommend both an in vitro $I_{Kr}$ assay (on either native $I_{Ks}$ or expressed hERG channels) and an in vivo QT assay as minimal components of an integrated drug assessment [67], whilst human testing must involve “thorough QT” studies that are typically conducted on healthy volunteers lacking baseline QTc prolongation [68,69]. No drug can be deemed safe for human use solely on the basis of non-clinical data alone [69]. The ICH E14 guidelines also note the importance of drug evaluation on human QT interval if a drug (or chemically/pharmacologically related compounds) has been associated with QT/QTc prolongation or torsades de point in post-marketing surveillance [68]. In accord with ICH E14, the FDA requested a thorough QT study, using sufficiently high doses of a drug in healthy volunteers and designed to detect small QTc changes (~ 5 msec) [69]. With this degree of prolongation, subjects are more prone to develop proarrhythmia [69]. However, it has not been proven that this degree of QTc prolongation is necessarily (i.e. deterministically) associated with torsades [69]. In this regard, the ICH E14 guidelines both note a lack of consensus in terms of upper limits to normal QTc and of changes from baseline and that, whilst the use of conservative lower limits might increase the risk of false positives, higher limits risk missing signals of concern [67]. The published human cardiac studies of QT interval, reviewed in section 4, clearly establish that ondansetron can prolong the QT interval, and there are also case-reports (section 5) that ondansetron can cause arrhythmias.
7.4 Parallels with droperidol and QTc prolongations and FDA

There are parallels between the present situation with ondansetron and the previous situation with droperidol, and its prolongation of QTc and the response of the FDA. Droperidol is a dopamine receptor antagonist that has been used as an antiemetic agent, but since 2001 has had a black box warning due to cases of QTc prolongation and/or torsades de pointes having been reported [70]. However, an independent analysis in 2007 of the evidence held by the FDA of 277 cases of adverse effects with droperidol, found that 85 of the cases were with the higher doses of droperidol being used as an antipsychotic in countries other than the USA [71]. Of the remaining reports, with the lower doses of droperidol being used as an antiemetic, many of the reports were found to be repeated up to 5 times, and only 2 described adverse effects with dosages used in the USA [71]. As a consequence of this, the black box warning for droperidol remains controversial [72,73,74,75], and parallels with the present situation with ondansetron have been made [76]. To avoid a similar ongoing controversy with ondansetron, we suggest that the FDA provide the evidence it has collected associating ondansetron to torsades for independent analysis as soon as possible, and elaborate on their reasoning for the black box warning.

7.5 Mechanism of QTc prolongation

From the evidence discussed in sections 3 and 5, it is reasonable to conclude that QTc prolongation by ondansetron results from direct repolarization-prolonging effects of the drug. As for most drugs associated with acquired Long QT syndrome [34,77], ondansetron inhibits Ikr/hERG [30,31]. In 2003, Redfern and colleagues proposed a provisional ‘safety margin’ for hERG blocking drugs of a >30-fold difference between hERG IC50 and maximum effective therapeutic concentration (unbound) [78]. Ondansetron has an I(hERG) blocking IC50 of 0.81 µM [31] and at plasma levels following intravenous administration of high drug doses [19], the cardiac safety margin for ondansetron may be unfavourable. It is nonetheless established that in a clinical setting, only a small proportion of patients receiving medications with Ikr/hERG blocking propensity tend to manifest clinically significant QTc prolongation and fewer still arrhythmia [76,77]. The extent to which ondansetron produces clinically significant QTc prolongation through Ikr inhibition is likely therefore to depend both on dose and route of administration (with a large dose administered intravenously presumably leading to a greater plasma concentration, facilitating Ikr block) and the presence of concomitant risk factors.

7.6 Mechanisms for other reported ECG changes

Ikr/hERG block may account for QTc prolongation with ondansetron but cannot explain the other ECG changes that are occasionally reported with ondansetron (section 6). The ability of the drug to
interact with sodium channels [30] may underpin the observed effects of the drug on the QRS complex, particularly under conditions such as ischaemia that may favour drug interactions with sodium channels in the inactivated state. Also, it has been reported that 5-HT₃ receptor activation may influence coronary arterial tone [79] and ondansetron use has been associated with coronary vasospasm [59,65]. Thus, acute ischaemia/ST segment elevation in patients without signs of established coronary vascular disease may be attributable to vasoconstrictor actions of ondansetron under some conditions.

### 7.7 Cardiovascular effects of the isomers

Ondansetron is a racemic drug, but the effects of the S(+) and R(−)-isomers on the QT interval have not yet been reported in a mainstream journal. However, data associated with a US patent supporting stereoselective use of ondansetron for apnoea are suggestive of a smaller effect of R-ondansetron than of the S-enantiomer or racemic drug form on canine QTc interval [80]. This is an important avenue for future investigation, as it is possible that the ability to prolong the QT interval is not uniform among the isomers, and that the cardiac safety may also differ between the isomers [81].

### 7.8 Palonosetron as an alternative to ondansetron

As the cardiac safety problems with ondansetron seem to be limited to the iv 32 mg dose used as prevention of the nausea and vomiting associated with chemotherapy, it would be advisable to use a different anti-emetic agent under these circumstances. Other “etrons” may also have the potential to prolong QTc, and the associated cardiac safety issues. Thus, dolasetron, a second generation 5-HT₃-receptor antagonist, has been shown to prolong QTc in subjects who are carriers for an allele that is associated with prolongation of QTc with 5-HT₃-receptor antagonists [82]. However, this is not a universal finding for the “etrons”.

Palonosetron, another second generation 5-HT₃ receptor antagonist, has been shown to be superior to ondansetron in preventing the nausea and vomiting associated with cancer chemotherapy [83,84]. Furthermore, recent studies have shown that palonosetron had no effect on QT interval in subjects with cancer [85,86,87]. This suggests that palonosetron is a more effective and safer option than ondansetron for preventing nausea and vomiting in subjects with cancer. Indeed, a recent review suggests that palonosetron should be the preferred 5-HT₃-receptor antagonist, in combination with a NK₁-receptor antagonist (e.g. aprepitant) and a dexamethasone, in highly emetogenic chemotherapy, and palonosetron with dexamethasone in moderate emetogenic
chemotherapy, despite palonosetron 0.25 mg iv costing US $407, compared to ondansetron 24 mg ~US $4 [88].

7.9 Conclusions

The dose of ondansetron that the FDA has concerns about is 32 mg iv (or several doses that are equivalent to this), which is only used in preventing nausea and vomiting associated with cancer chemotherapy. This suggests that ondansetron may be safe in the lower doses used to prevent the nausea and vomiting in radiation treatment or postoperatively. However, as there is a report that ondansetron 4 mg iv prolonged the QT interval in health volunteers [46], this needs to be clarified by the FDA. More research needs to be undertaken of the relationship between QT prolongation and torsades in order that the FDA can produce clear-cut evidence of pro-arrhythmic risk when introducing black box warnings for this.

As ondansetron is an effective anti-emetic, questions arise regarding what can be done to mitigate potential cardiac risk? Further work is required to establish whether or not single enantiomer preparations of ondansetron may in the future offer a viable alternative to the racemic drug. As the FDA have rightly pointed out, the drug should be used with caution in patients with heart failure or identified risk factors for QT prolongation and, additionally, electrolyte abnormalities should be corrected before use. For cancer patients who might previously have been treated with 32mg/iv ondansetron, or who possess other risk factors for QTc prolongation, palonosetron may offer a safer alternative to ondansetron for prevention of nausea and vomiting.

References


5. FDA Drug Safety Communication: Abnormal heart rhythms may be associated with the use of Zofran (ondansetron) [http://www.fda.gov/Drugs/DrugSafety/ucm271913.htm#data] Accessed 13/12/2012


**FDA alert of QT prolongation with ondansetron**


**Important preclinical electrophysiology study of ondansetron


**Important preclinical electrophysiology study of ondansetron


*One of the early studies showing ondansetron prolonged QTc in humans


**Important study characterising the prolongation of QTc by ondansetron in humans


*Study showing that a low dose of ondansetron prolonged QTc in healthy humans


**Important study characterising the prolongation of QTc by ondansetron in humans with cardiovascular disease


*First report of prolongation of ventricular arrhythmia with ondansetron in child with LQTS


*Important study linking ondansetron with arrhythmias in children with LQTS


*Independent analysis of the FDA data for droperidol raising concerns about the necessity for a black box warning


73. Ludwin DB, Shafer SL. Con: the black box warning on droperidol should not be removed (but should be clarified!). Anesth Analg 2008;106(5):1418-20.


75. Faine B, Hogrefe C. News flash. Old Mother Hubbard reports the cupboard is bare…time for the FDA to let droperidol out of the (black) box. Ann Pharmacother 2012;46(9):1259-61.


