In Reply: Evidence for Equivalent Cardiotoxicity of the 5-HT₃ Receptor Antagonists

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The response by Dr. Ellis and Dr. Dozier to our article and that of Dr. Keefe’s, which recently appeared in The Oncologist [1-3], suggests that the available antiemetics in this class—granisetron, ondansetron, and dolasetron—share a similar cardiovascular side-effect profile. Although their conclusions are worthy of consideration, I would like to also highlight additional information.

It is suggested that alterations in electrocardiographic (ECG) intervals are a class effect. While it was acknowledged in our original manuscript [1] that the class of 5-HT₃ receptor antagonists has been reported to produce small, statistically significant, but clinically asymptomatic, changes in ECG parameters, the susceptibility for inducing cardiac effects varies among these agents. Additionally, in discussing the cardiovascular effects, we focused our paper on QTc prolongation, and not ECG changes in general. We do not dispute that the data for dolasetron are comprehensive nor that the frequency of small transient ECG changes with dolasetron is comparable with other 5-HT₃ receptor antagonists; however, it is the magnitude of these changes with escalating doses or increased plasma concentrations, secondary to potential drug-drug interactions, of dolasetron that give cause for concern. We agree that after 24 hours following administration of 5-HT₃ receptor antagonists, equivalent alterations in cardiac conduction intervals have been demonstrated, suggesting a class effect. However, during the first 1-2 hours after drug administration, dolasetron has been shown to produce greater changes in these parameters than either granisetron [4] or ondansetron [5]. Specifically, patients receiving dolasetron, 1.8 and 2.4 mg/kg i.v., had significantly greater (p = 0.0016) increases in QTc interval than patients administered granisetron at the high European dose (3 mg i.v.) [4]. As stated in our original review, there is a known validated link between QTc elongation and cardiovascular risk in the form of torsades de pointes, which can sometimes prove fatal. We agree the risk is likely minimal following dolasetron monotherapy in healthy patients; however, in reality, patients receive their 5-HT₃ receptor antagonists as part of a polypharmacy regimen. It is in this patient population that we recommend caution be taken regarding the risk of drug interactions for all medications, including the 5-HT₃ receptor antagonists. Of additional concern is that cancer is a disease of the elderly, and it has been documented that the majority of elderly cancer patients with comorbid conditions are receiving multiple medications [6, 7]. Many of these medications possess cardiovascular warnings. Therefore, consideration must be given to the possibility of in vivo drug-drug interactions in individual patients and the risk from concomitant medications that may produce additive QTc interval prolongations.

The metabolism of the 5-HT₃ receptor antagonists is an area we feel has been overlooked by many in contributing to the toxicities of this class of drugs, including the cardiovascular effects. The hepatic isozyme cytochrome P450 (CYP)2D6 becomes important when evaluating drug interactions and in patients that are phenotypically poor metabolizers [8], which we briefly reviewed in our original manuscript [1]. Poor metabolizers, in particular, must be considered at higher risk of drug-drug interactions that may impact cardiac conduction intervals. Even in a very small pharmacokinetic study of
dolasetron with 24 healthy males, one participant was identified as a CYP2D6 poor metabolizer, having a urinary metabolite level that differed markedly from the other participants [9]. Theoretically, he was at high risk for a potential drug-drug interaction due to prolonged concentrations of the active metabolite of dolasetron in his body. Indeed, in this particular individual, the area under the curve was calculated as 1.9-2.3 times higher than the mean of the other 23 participants. This again highlights the consideration of the metabolism of these agents and subsequent greater risk of toxicities, including cardiovascular, secondary to a greater area under the curve of the active drug.

As we [1] and Keefe [2] reported previously, dolasetron results in dose-dependent changes in cardiac conduction intervals. For example, Grote reported statistically significant ($p < 0.001$) linear trends for increased PR, QTc, and QRS intervals on ECG tracings appearing 1-2 hours following administration of oral dolasetron (25, 50, 100, or 200 mg) [10], and we also cited literature that reported a dose-related increase in QTc interval following i.v. dolasetron (1.2, 1.8, and 2.4 mg/kg; $p < 0.001$) [11]. This is particularly relevant since some investigators suggest that the approved dose of oral dolasetron (100 mg) [12] may be suboptimal [10, 13, 14], and therapeutic guidelines [15] cited by Ellis and Dozier recommend the use of 100-200 mg dolasetron.

Ellis and Dozier interpreted the data by Kurysh et al. [16] and de Lorenzi et al. [17] that examined the interactions of the 5-HT$_3$ receptor antagonists with human and feline cardiac ion channels, respectively. We agree with the study results that dolasetron has less antagonist activity than granisetron on the sodium ion channel and less activity than either granisetron or ondansetron on the potassium ion channel. It is important to note that Kurysh and his colleagues, in their discussion, related their findings to the clinical doses and subsequent plasma levels utilized to control chemotherapy-induced nausea and vomiting to determine the clinical relevance of these in vitro studies [16]. The administration of granisetron 3 mg i.v. (the European dose) results in a plasma concentration 35-fold lower than the 50% inhibitory concentration (IC$_{50}$) utilized by Kurysh et al. for sodium channel blockade, while the administration of dolasetron 200 mg i.v. resulted in a plasma concentration of hydrodolasetron that was 8.5-fold lower than the IC$_{50}$ utilized by Kurysh et al. [16]. In a patient who is CYP2D6 deficient, or in a patient where a drug-drug interaction results in increased blood levels, as has been reported with cimetidine [12], or decreased clearance, as reported with atenolol [18] when coadministered with dolasetron, the risk for sodium channel blockade may be higher for dolasetron, again highlighting the need for evaluation of potential drug-drug interactions.

Also mentioned in their letter, Ellis and Dozier provide statistics from US Oncology suggesting that dolasetron is used in 95% of patients requiring a 5-HT$_3$ receptor antagonist. Cardiovascular disease is a major cause of comorbidity and mortality in older patients with cancer [19]. This reiterates our point that physicians are using this agent in all patients—a large proportion of whom will be elderly with cardiovascular impairments—despite documented cardiac warnings in the package insert [12]. In addition, while we do not dispute the Ellis and Dozier’s concluding remarks that “dolasetron is the 5-HT$_3$ receptor antagonist most thoroughly studied for cardiac effects,” we would urge the prescriber of any medication to assess the side effects and potential complications of each agent on an individual patient basis. The purpose of our original manuscript was to serve as a comprehensive review of the side-effect profiles of each 5-HT$_3$ receptor antagonist so that the reader was able to make an informed decision on which antiemetic agent to choose for particular patients, taking into consideration their possible underlying comorbidities.

**REFERENCES**


15 ASHP therapeutic guidelines on the pharmacologic management of nausea and vomiting in adult and pediatric patients receiving chemotherapy or radiation therapy or undergoing surgery. Am J Health Syst Pharm 1999;56:729-764.


