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Measurement of Early and Late Repolarization Periods in Addition to QT Interval to Help Predict the Torsadogenic Risk of Donepezil Based on Reverse Translational Animal Research on Its Proarrhythmic Potential

To the Editor:

Donepezil, a cholinesterase inhibitor used to treat Alzheimer's disease, has been shown to induce QT prolongation and torsade de pointes (TdP) in patients with multiple risk factors, including older age, female sex, cardiovascular comorbidities, and concomitant medications.[1–8] Because it is possible that donepezil alone lacks torsadogenic potential but that these other precipitating factors could compound its I_{Kr} inhibitory action, we read with great interest the article by Kuwahata et al, who showed that the incidence of corrected QT interval (QTc) prolongation was greater in patients taking donepezil than in control subjects not taking donepezil despite similar background characteristics.[9] Although the findings of Kuwahata et al will make physicians pay attention to electrocardiogram monitoring of patients taking donepezil, the authors did not necessarily provide specific information to predict which patients with QTc prolongation may actually be at risk of the onset of TdP.

To this end, our recent experimental findings[10] would help to estimate the magnitude of torsadogenic risk of donepezil in patients reported by Kuwahata et al. We used 2 different types of canine models,[10] namely the halothane-anesthetized dogs with the intact hearts, which can mimic the drug-induced electrophysiological responses in healthy human subjects, and the conscious chronic atrioventricular block dogs with the pathologically remodeled hearts, a well-established proarrhythmia animal model.[11] First, we analyzed the effects of donepezil on the QT interval of the anesthetized dogs.[10] We also separately measured the early ($J\text{-}T_{peak}$) and late ($T_{peak}\text{-}T_{end}$) repolarization periods, which are proarrhythmic surrogate markers originally developed for human subjects.[12] $J\text{-}T_{peak}$ can estimate the net balance between inward $I_{Na,L}$ plus $I_{Ca,L}$ and outward I_{Ks} plus I_{Kr} during Phase 2 of the action potential, and a prolongation in $J\text{-}T_{peak}$ may predict the onset of Ca^{2+} overload, governing the "trigger" of premature ventricular contractions.[13] Meanwhile, $T_{peak}\text{-}T_{end}$ may indicate the extent of I_{Kr} inhibition, with a prolongation in $T_{peak}\text{-}T_{end}$ possibly reflecting an increase in transmural dispersion of the repolarization period, which also plays an important role as a "substrate" for perpetuating spiral re-entry.[12,14] Intravenous administration of 1 mg/kg donepezil hydrochloride over 10 min, which provided an approximate 30-fold greater plasma concentration than the clinically effective concentration, modestly prolonged the QT/QTc and $T_{peak}\text{-}T_{end}$, suggesting that donepezil may suppress I_{Kr} in the heart. More importantly, it significantly prolonged the corrected $J\text{-}T_{peak}$ ($J\text{-}T_{peak}c$), which indicates that donepezil can prolong Phase 2 repolarization of the action potential, possibly inducing Ca^{2+} overload in the normal heart.

Second, we tried to demonstrate the causal link between the administration of donepezil and the onset of TdP using the chronic atrioventricular block dog model.[10] The same dose of donepezil as used in the anesthetized dogs did not induce TdP, but caused non-sustained ventricular tachycardia in 2 of 4 animals. The onset of ventricular tachycardia may be closely associated with Ca^{2+} overload, which could be expected by the significant prolongation of $J\text{-}T_{peak}c$ in the anesthetized dogs. Meanwhile, the lack of induction of TdP in the chronic atrioventricular block dogs suggests that I_{Kr} suppression by donepezil alone may not be enough to provide a "substrate" for perpetuating spiral re-entry, which was expressed by the modest $T_{peak}\text{-}T_{end}$ prolongation in the anesthetized dogs. These results suggest that donepezil by itself can induce a "trigger" for the onset of TdP, but it does not necessarily provide a "substrate" for perpetuating TdP. Thus, simultaneous measurement of early and late repolarization periods, along with the QT interval, may improve the sensitivity and specificity of predicting the onset of drug-associated TdP in patients with pre-existing multiple risk factors.

In effect, in our reverse translational animal studies, donepezil alone significantly prolonged $J\text{-}T_{peak}c$, along with modest prolongation of QT/QTc and $T_{peak}\text{-}T_{end}$, in the normal hearts and induced ventricular tachycardia without degenerating into TdP in the pathologic hearts. In donepezil-treated patients, $J\text{-}T_{peak}c$ and $T_{peak}\text{-}T_{end}$ should be measured simultaneously in addition to QTc to separately quantify the "substrate" and "trigger" to predict the torsadogenic risk, because pre-existing multiple risk factors in patients should modify these proarrhythmic surrogate markers.

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Disclosures

The authors have no conflicts of interest to declare.

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AUTHOR'S REPLY

Measurement of Early and Late Repolarization Periods in Addition to QT Interval to Help Predict the Torsadogenic Risk of Donepezil Based on Reverse Translational Animal Research on Its Proarrhythmic Potential — Reply —

We read with great interest the Letter to the Editor from Kambayashi et al. We thank them for their insightful comments regarding our recent article.[1] In a previous study, these authors analyzed the effect of donepezil on the QT interval by separately measuring the early (J-T_{peak}) and late (T_{peak}-T_{end}) repolarization periods in canine models. Intravenous administration of 1 mg/kg donepezil hydrochloride significantly prolonged the corrected J-T_{peak}, in addition to modestly prolonging T_{peak}-T_{end}.[2] Kambayashi et al suggested that, in donepezil-treated patients, simultaneous measurement of the early and late repolarization periods, along with the QT interval, may predict the onset of drug-associated Torsade de pointes.

In our study, we investigated the correlation between patients' background characteristics or blood biochemical findings and the corrected QT (QTc) interval in patients taking donepezil. On univariate analysis, QTc was associated with hemoglobin, serum calcium concentration, and the estimated glomerular filtration rate (eGFR). On multivariate analysis, serum potassium concentration and eGFR were significantly associated with QTc.[1] However, as Kambayashi et al point out, it was difficult to predict which of the patients taking donepezil would have QTc prolongation.

The T_{peak}-T_{end} interval serves as an index of transmural dispersion of repolarization.[3] Prolongation of the T_{peak}-T_{end} interval was previously demonstrated in patients with hypertrophic cardiomyopathy,[4,5] and has been reported to be a risk factor for ventricular fibrillation in patients with Brugada syndrome.[6] In addition, prolongation of the T_{peak}-T_{end} interval was associated with an increased risk of sudden cardiac death.[7]

We agree with the suggestion of Kambayashi et al to measure and evaluate J-T_{peak} and T_{peak}-T_{end} to predict fatal arrhythmias in patients taking donepezil. However, there are some debatable points that need to be resolved in the

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