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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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future. First, the previous study Kambayashi et al refer to was an animal experiment in canines, and it is unclear whether the results can be extrapolated to humans.[2] Second, their study involved plasma concentrations that were 30-fold higher than the clinically effective concentrations.[2] In that study, Kambayashi et al said that intravenous administration of donepezil hydrochloride at concentrations as high as 1 mg/kg may have reached toxicological concentrations that could induce respiratory arrest in the anesthetized dogs.[2] Further clinical studies within the effective plasma concentration range for humans are needed to prove this result in a clinical setting. Third, it is difficult to measure the QT interval separately for the early and late periods; it may not be easy for everyone to do. T-wave morphology has substantial changes, such as flattened or notched T-waves.[8] In the study of Kambayashi et al, when the end of the T wave was unclear, the end was estimated using the monophasic action potential signal as a guide.[2] An ambiguous definition of the peak of the T-wave can cause large variations in measurements.[8] Therefore, the objectivity of the measured values may not be maintained and may not be suitable for screening that needs to be performed within a short time. Automatic measurements of J-T_{peak} and T_{peak}-T_{end} intervals have already been reported,[8] but are not yet commonly used. We hope that electrocardiograms will be equipped with automatic measurement of J-T_{peak} and T_{peak}-T_{end} intervals, and that screening will become widespread.

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