ORIGINAL ARTICLE

Empagliflozin significantly attenuates sotalol-induced QTc prolongation in rats

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KEY WORDS
empagliflozin, sotalol, QTc prolongation

ABSTRACT

BACKGROUND Sotalol is a class III antiarrhythmic drug commonly used in various arrhythmia treatments. However, due to its potent potassium channel inhibition, it can prolong the QT interval and lead to malignant arrhythmias. Empagliflozin is an inhibitor of sodium-glucose cotransporter 2 (SGLT2) and has a positive effect on cardiovascular outcomes. Since the effect of empagliflozin on the activation of potassium channels is unknown, there is no recommendation regarding the coadministration of these drugs.

AIMS The study aimed to evaluate the possible protective effects of empagliflozin on sotalol-induced QT prolongation.

METHODS We randomized 24 rats into 4 groups. The control group received only physiological saline, the EMPA group, empagliflozin; the SOT group, sotalol; and the EMPA+SOT group, empagliflozin and sotalol. PR and QT intervals and heart rates were measured under anesthesia at baseline and at 1, 2, and 3 hours in lead II.

RESULTS In the SOT group, the QT and QTc intervals as well as T-wave duration were statistically longer, whereas heart rates were lower than in the control group (P <0.001 for all parameters). Empagliflozin ameliorated sotalol-induced QT and QTc prolongation in the EMPA+SOT group. The QT interval, T-wave duration, and QTc interval were shorter, and the heart rate was greater than in the SOT group (P <0.001, P = 0.002, P <0.001, and P <0.001, respectively).

CONCLUSIONS Empagliflozin significantly ameliorates sotalol-induced QT prolongation and could be used safely with sotalol in clinical practice. Future clinical trials might recommend the routine use of empagliflozin to prevent QTc prolongation in diabetic patients receiving sotalol.

INTRODUCTION Sotalol is a class III antiarrhythmic drug that acts by blocking the rapid potassium (IKr) channel.[1] In clinical practice, sotalol is indicated for many conditions, such as ventricular tachycardia, atrial fibrillation, and supraventricular tachycardia. However, its use is limited because it increases mortality by inducing QT prolongation.[1,2]

Empagliflozin is a selective sodium-glucose cotransporter 2 (SGLT2) inhibitor used in patients with type 2 diabetes.[3] Prospective randomized clinical trials have shown that empagliflozin prevents cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke in diabetic patients at high cardiovascular risk.[4] Current guidelines recommend empagliflozin as a first-choice drug in diabetes treatment.[5] In animal studies, empagliflozin has been shown to exert effects especially on sodium (sodium–hydrogen exchanger) and calcium (L-type, SERCA2a) ion channels.[6,7]

However, the effect of empagliflozin on IKr channel, which plays a key role in phases 2 and 3 of the cardiac action potential, is not yet known. Therefore, there are no data on its potential use with class III antiarrhythmic drugs. This study aimed to explore the clinical conditions that may arise from the coadministration of sotalol and empagliflozin, which may be coadministered in the same patient group.

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WHAT'S NEW?

The effect of empagliflozin on rapid or slow potassium channels, which plays a key role in phases 2 and 3 of the cardiac action potential, is not yet known. Therefore, there is no information on its potential use with class III antiarrhythmic drugs, such as sotalol. This study shows that empagliflozin prevents sotalol-induced QT prolongation. Most probably, empagliflozin may exert this effect by regulating the intracellular sodium and calcium balance and possibly promoting potassium channel activation. Our findings indicate that empagliflozin could be used safely with sotalol in clinical practice.

METHODS **Experimental animals** Twenty-four male Wistar Alba rats (age range, 20–25 weeks; weight range, 350–400 g) obtained from Kobay A.Ş. (Ankara, Turkey) and housed in the Physiology Department of Hacettepe University, Ankara, Turkey were used in this study. In this study, healthy male rats were used to prevent the probable effects of diabetes and menstrual cycle on QTc.[8,9] All rats were kept under controlled conditions at 21 °C (range, 19 °C–23 °C) and 30% to 70% relative humidity. The animals were maintained on a 12-hour light/12-hour dark cycle (the lights were on between 7 AM and 7 PM) with ad libitum access to tap water and a standard rat chow diet. The study was approved by the Hacettepe University School of Medicine Institutional Ethics Committee for Animal Experiments (no. 2019/32, July 9, 2019). All experimental procedures conformed to the Guiding Principles for the Care and Use of Laboratory Animals.

Experimental protocol The animals were randomized into 4 groups of 6. The first (control) group received physiological saline (1 ml) via an orogastric tube. The second (EMPA) group received empagliflozin (10 mg/kg; Jardiance, Boehringer Ingelheim, Ingelheim am Rhein, Germany) via an oral tube. The third (SOT) group received l-sotalol (80 mg/kg; Darob, Abbott, Istanbul, Turkey) via an oral tube. The fourth group (EMPA+SOT) received l-sotalol (80 mg/kg) and empagliflozin (10 mg/kg) via an oral tube. All drugs were suspended in physiological saline.

Electrocardiography All animals were anesthetized with intraperitoneal injection of ketamine (40 mg/kg; Ketalar, Pfizer, Istanbul, Turkey) and xylazine hydrochloride (4 mg/kg; Alfazyne 1, Alfasan International, Woerden, The Netherlands) at baseline and at 1, 2, and 3 hours. They were then fixed in the prone position, and electrocardiograms (ECGs) were obtained from the D2 lead with needle electrodes (Supplementary material, *Figure S1*). The ECGs were evaluated with the Biopac MP36 system (Biopac Systems, Goleta, California, United States). The PR and QT intervals, T-wave duration, and heart rates (HRs) were measured by examining the ECGs at baseline and at 1, 2, and 3 hours. After the QT interval and HR measurements were performed, the corrected QT (QTc) interval was calculated with the Bazett formula ($QT / \sqrt{R\text{-}R}$).

Statistical analysis Statistical analyses were performed with IBM SPSS Statistics 22 (IBM, Armonk, New York, United States). The Shapiro–Wilk test was used to evaluate whether data fit the normal distribution. Data with normal distribution were expressed as means (SD), and data with distribution other than normal were expressed as medians and interquartile ranges. All ECG parameters at all available time-points (baseline, hour 1, 2, and 3) were compared with repeated analysis of variance (ANOVA) measurements followed by the Tukey post-hoc test (in a single analysis). Electrocardiogram parameters of all study groups at each time point (baseline, hour 1, 2, and 3) were separately compared using the Kruskal–Wallis test, followed by Nemeyni post hoc test for nonnormally distributed data (QTc and HR at baseline and QTc at hour 1) or 1-way ANOVA, followed by the Tukey post hoc test for normally distributed data (all of other parameters). A P value of less than 0.05 was considered statistically significant.

RESULTS Supplementary material, *Table S1* presents a comparison of ECG measurements between all groups at baseline and at 1, 2, and 3 hours. Further differences were observed between the SOT group and other groups when changes in HR, QT and QTc intervals, and T-wave duration of the groups were compared at baseline and after 1, 2, and 3 hours with repeated ANOVA measurements followed by the Tukey post-hoc test (P <0.001 for interaction between time and groups for all parameters).

The QT and QTc intervals, T-wave duration, and HR were similar between groups at baseline. The QT interval and T-wave duration were statistically longer and HR was shorter in the SOT than in the control group (P <0.001; P <0.001; P = 0.019 for all parameters) at 1 hour. However, the QT interval was shorter in the SOT+EMPA group than in the SOT group (P <0.001; P <0.001; P = 0.019 for all parameters, respectively) at 1 hour.

The differences in QT, QTc, and HR values between the SOT and control groups were observed most clearly after 2 hours (FIGURES 1–3). The QT interval, T-wave duration, and QTc interval were statistically longer, and the HR was lower in the SOT than in the control group (P <0.001 for all parameters). The mean (SD) PR interval was 54.8 (4.7) ms, the QT interval was 81.6 (5.9) ms, the T-wave duration was 42.3 (4.7) ms, the HR was 332.0 (18.3) bpm, and the QTc interval was 191.54 (10.5) ms. The ECG findings in the EMPA group were within normal limits and similar to those of the control group.

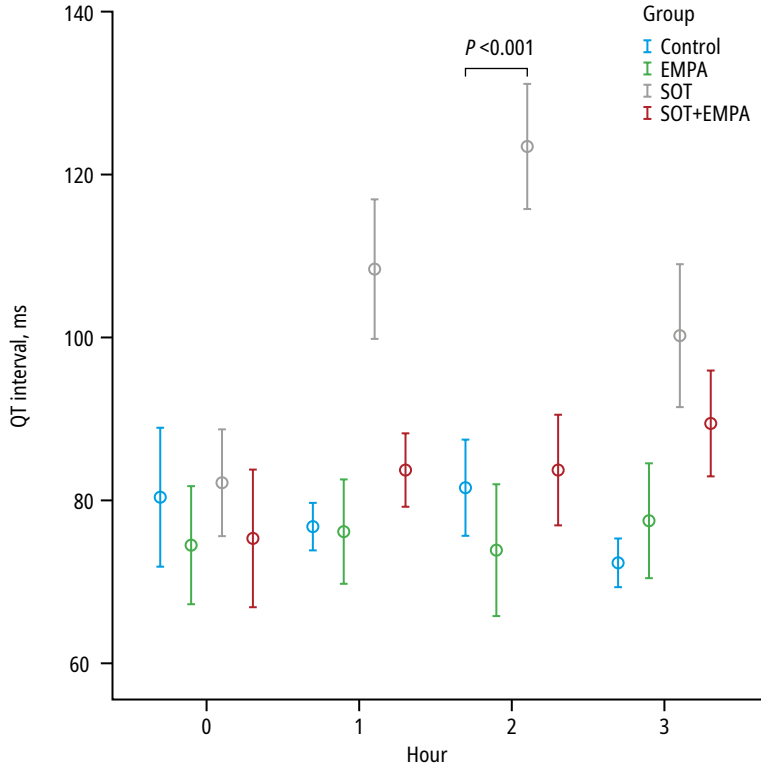

FIGURE 1 QT comparisons for all groups. The most considerable differences in QT values between the sotalol group and the control group could be observed after 1 and 2 hours. Circles indicate means, bars indicate SD. The 1-way analysis of variance, followed by the Tukey test, was applied.

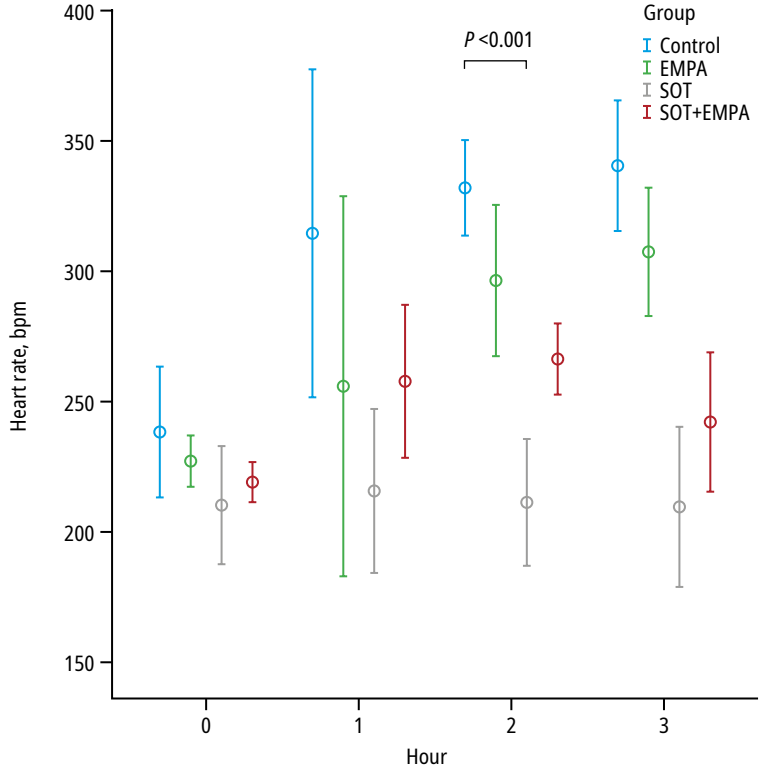

FIGURE 2 Heart rate comparisons for all groups. The most considerable difference in HR between the sotalol group and the control group could be observed after 2 hours. Circles indicate means, bars indicate SD. The 1-way analysis of variance, followed by the Tukey test, was applied.

Empagliflozin ameliorated sotalol-induced QT and QTc prolongation in the EMPA+SOT group. The QT interval, T-wave duration, and QTc interval were shorter (P <0.001, P = 0.002 and P <0.001, respectively), while the HR was higher than in the SOT group (P <0.001). The PR interval was similar in all 4 groups. Comparisons of ECG measurements for 1 second within the second hour between all groups are shown in Supplementary material, *Figure S2*. A distinct QT interval and especially T-wave prolongation can be seen in the SOT group.

DISCUSSION

This study found that empagliflozin significantly ameliorated sotalol-induced QT prolongation. In the SOT group, sotalol-induced QT and QTc interval and T-wave prolongation was most evident after 2 hours, which is in line with the available literature.[10] This effect was significantly weaker in the EMPA+SOT group. The measurements in the control group were within normal limits and consistent with the literature.[8]

Sotalol is indicated for many arrhythmic conditions.[1] Besides its weak β-blocking activity, it acts mainly by blocking the IKr channel. This leads to the prolongation of phase 2 and 3 of cardiac action potential. This effect manifests as QTc interval and T-wave prolongation in ECG. Sotalol can lead to a 65% increase in mortality due to QTc interval prolongation caused by cardiac action potential prolongation in patients with left ventricular dysfunction after a recent or older myocardial infarction.[2] This potential adverse event limits its clinical use.

Empagliflozin is a new selective SGLT2 inhibitor used in patients with type 2 diabetes.[3] It exerts its antidiabetic effect by decreasing glucose absorption and increasing glycuresis due to its inhibition activity in the SGLT2 channel of the kidney proximal tubule.[3] The EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) clinical trial showed that empagliflozin reduces the primary endpoints, including death, nonfatal myocardial infarction, and nonfatal stroke, in type 2 diabetic patients at high cardiovascular risk.[4] Furthermore, the EMPEROR-Reduced Trial (Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure) showed that empagliflozin reduces cardiovascular death or hospitalization for heart failure in heart failure patients with or without diabetes mellitus.[9] Empagliflozin has consequently been recommended as the first-choice drug for cardiovascular protection in diabetes treatment.[5] However, the mechanism of its observed positive effect has not been fully explained. It has been suggested that its clinical benefit may be associated with its positive effects on arterial stiffness, cardiac oxygen demand, albuminuria, visceral adiposity, and blood pressure.[10-13]

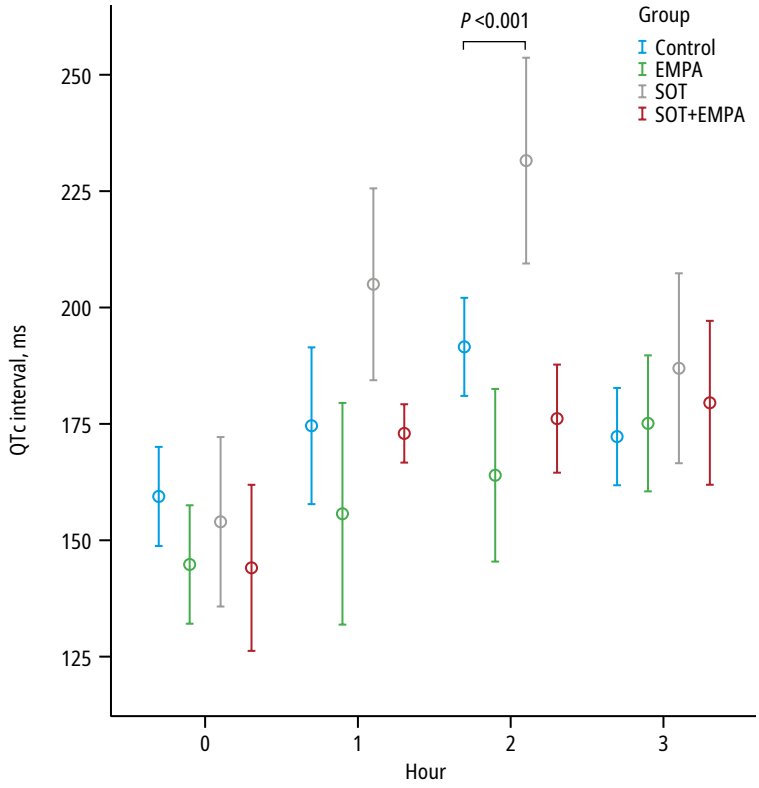

FIGURE 3 QTc comparisons for all groups The most considerable differences in QTc values between the sotalol group and the control group could be observed after 2 hours. Circles indicate means, bars indicate SD. The 1-way analysis of variance, followed by the Tukey test, was applied.

In heart failure and ischemia animal models, empagliflozin has been shown to markedly improve systolic and diastolic dysfunction,[14,15] left ventricular fibrosis,[16] and left ventricular remodeling.[17] In a diabetes model, it had positive effects on calcium channel dysfunction (L-type channel activation, SERCA2a upregulation).[6] However, it is not known whether empagliflozin has any direct or indirect effect on potassium channels. Therefore, the consequences that may arise from combining empagliflozin with class III antiarrhythmic drugs acting through strong potassium channel inhibition are unknown.

The protective effect of empagliflozin against sotalol-induced QT prolongation may be attributed to several mechanisms. First, Baartscheer et al[7] showed that, apart from inhibiting SGLT, empagliflozin reduces cytosolic sodium concentrations by increasing the cardiac sodium–hydrogen exchange activity. It is also known that sotalol prolongs the action potential duration and the QTc interval by blocking potassium channels without affecting sodium channel activity. In our study, empagliflozin may have prevented sotalol-induced QTc prolongation by reducing the concentration of cytosolic sodium and duration of myocardial depolarization as well as by balancing the potassium channel blockade.

Second, in a streptozotocin-induced diabetes model, Lee et al[6] found that while empagliflozin promoted L-type calcium channel activation, sodium–calcium exchanger pump activity, and SERCA2a and RYR2 protein expression, it decreased late sodium channel activation and RyR2-pS2808 protein levels. Empagliflozin thus shortened the QT interval by reducing calcium sparks, thereby shortening the duration of action potential.[6] The protective effect of empagliflozin against sotalol-induced QT prolongation, also seen in our study, may be due to shortening of the action potential duration via regulation of intracellular calcium.

Third, our findings suggest that empagliflozin may prevent solatol-induced QT prolongation caused by strong potassium channel blockage by promoting the activation of potassium channels. Sotalol-induced QT interval prolongation is caused especially by T-wave prolongation. Empagliflozin has an opposite effect primarily by shortening the T wave. It is known that the T wave in ECG corresponds to phase 3 of the action potential, and its duration and amplitude are determined by the activation of the rapid and slow potassium channels. Thus, our results indicate that empagliflozin may have an effect on potassium channels.

No large studies have evaluated the effect of empagliflozin on the QT interval. Our literature search yielded only a small-scale study, which reported that empagliflozin does not cause significant QT prolongation compared with moxifloxacin.[18] We found no studies on the possible effect of empagliflozin when administered with drugs that prolong the QT interval, such as class III antiarrhythmics, antidepressants, and antihistamines.

Our study shows that when empagliflozin is used in combination with sotalol, it can prevent the latter's dangerous side effects. This suggests that empagliflozin could be used safely in diabetic patients who are prone to sotalol-induced QTc interval prolongation.[19]

The most important limitation of this study is that it was not biophysical, and the channel activities could not be directly evaluated with the voltage clamp technique. Biophysical voltage clamp studies are needed to establish the effects of empagliflozin on the potassium channels directly.

Conclusions Our study shows that empagliflozin prevents sotalol-induced QT prolongation. Empagliflozin may exert this effect by regulating the intracellular sodium and calcium balance and possibly promoting potassium channel activation. Our findings indicate that empagliflozin could be used safely with sotalol in clinical practice. Future clinical studies might lead to recommendations suggesting the routine administration of empagliflozin for the prevention of QTc-interval prolongation in diabetic patients treated with sotalol.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/kardiologiapolska.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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