Cardiovascular Topics

Empagliflozin significantly prevents QTc prolongation due to amitriptyline intoxication

Veysel Özgür Barış, Esra Gedikli, Adnan Berk Dinçsoy, Ayşen Erdem

Abstract

Aim: Empagliflozin (EMPA) is a sodium-glucose transporter-2 inhibitor used in the treatment of type 2 diabetes and has positive effects on cardiovascular outcomes. Amitriptyline (AMT) can be used in many clinical indications but leads to cardiotoxicity by causing QT prolongation. Our aim in this study was to determine how the effects of the concomitant use of empagliflozin and amitriptyline, which have been shown to have effects on sodium and calcium metabolism in cardiomyocytes, would cause an effect on QT and QTc intervals in clinical practice.

Methods: Twenty-four male Wistar albino rats were randomised into four groups. The control group received only physiological serum (1 ml) via orogastric gavage (OG). The EMPA group received empagliflozin (10 mg/kg) via OG. The AMT group received amitriptyline (100 mg/kg) via OG. The AMT+EMPA group (n = 6) received amitriptyline (100 mg/kg) and empagliflozin (10 mg/kg). Under anaesthesia, QT and QTc intervals were measured at baseline, and in the first and second hours.

Results: In the AMT group, QT intervals and QTc values were found to be statistically longer than in the control group ($p \leq 0.001$). Empagliflozin significantly ameliorated amitriptyline-induced QT and QTc prolongation. In the AMT+EMPA group, QT and QTc intervals were significantly lower compared to that in the AMT group ($p < 0.01$)

Conclusion: In this study, we determined that empagliflozin significantly ameliorated amitriptyline-induced QT and QTc prolongation. This effect was probably due to the opposite effects of these two agents in the intracellular calcium balance. With more clinical trials, the routine use of empagliflozin may be suggested to prevent QT and QTc prolongation in diabetic patients receiving amitriptyline.

Keywords: empagliflozin, amitriptyline, QTc prolongation

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Physiology Department, Hacettepe University, Gaziantep, Turkey

Veysel Özgür Barış, MD, veyselozgurbaris@gmail.com
Esra Gedikli, MD
Adnan Berk Dinçsoy, MD
Ayşen Erdem, MD

Empagliflozin (EMPA) is a selective sodium-glucose transporter-2 (SGLT-2) inhibitor used in patients with type 2 diabetes mellitus (DM).[1] There are data showing that EMPA reduces cardiovascular mortality in patients with type 2 DM in addition to its antidiabetic effects.[2] Although there is not yet a physiopathological explanation for these positive effects of EMPA, it has been shown that EMPA causes changes in the intracellular sodium (Na) and calcium (Ca) balance and in the duration of action potentials in cardiomyocytes, regardless of SGLT-2 inhibition.[3,4]

Tricyclic antidepressant (TCA) drugs can be used in many situations in clinical practice. However, TCA may cause cardiotoxicity that leads to high rates of mortality and morbidity, and AMT is the most common agent causing TCA toxicity.[5,6] AMT may cause cardiotoxicity due to ventricular arrhythmias caused by its Na channel inhibition and changes in intracellular Ca metabolism.[7,8] The toxicity caused by TCA is dose independent and this toxicity manifests itself with prolongation in PR, QT and QTc intervals, measured on the ECG.[9] QT prolongation on ECG is a predictor for toxicity and indicates a poor prognosis.[10]

In this study, we aimed to determine how the effects of the concomitant use of EMPA and AMT, which are used in the treatment of type 2 DM and which have been shown to have effects on Na and Ca metabolism in cardiomyocytes, could cause an effect on QT and QTc intervals in clinical practice.

Methods

Twenty-four male Wistar albino rats (350–400 g) obtained from Kobay AŞ (local corporation) and housed in the Physiology Department of Hacateppe University was used for this study. All rats were kept under controlled conditions at 21 ± 2°C and 30–70% relative humidity with 12-h dark/12-h light illumination sequence (the lights were on between 07.00 and 19.00) with *ad libitum* access to tap water and standard rat chow.

The study was approved by the Hacateppe University School of Medicine institutional ethics committee for animal experiments (dated 11/11/2019 and numbered 2019/12-02). All the study procedures were performed according to the Guiding Principles for the Care and Use of Laboratory Animals.

The experimental animals were randomised into four groups. The first group was the control group (n = 6) and physiological serum (1 ml) was administered to the animals of this group via an orogastric tube. The second group was the EMPA group and EMPA (10 mg/kg, Jardiance, Boehringer Ingelheim) was administered to the animals of this group via an orogastric tube (based on a previous study[11]) (Fig. 1A).

The third group was the AMT group and AMT (100 mg/kg; Laroxyl 25 mg, Roche) was administered to the animals of this group via an orogastric tube (based on a previous study[12]). The fourth group was the AMT+EMPA group and AMT (100 mg/kg) and EMPA (10 mg/kg) were administered to the animals of this group via an orogastric tube. All drugs were suspended in physiological serum.

Tablets containing 10 mg active EMPA (Jardiance, Boehringer Ingelheim) and 25 mg AMT (100 mg/kg, Laroxyl 25 mg, Roche), which weighed nearly 257 mg and 194.6 mg with other supplemental products, respectively, were dissolved in physiological serum to yield a concentration of 5 mg/ml and 50 mg/ml, respectively. According to the weight of each rat, the suspended drug solution was completed to 2 ml with physiological serum.

All subjects were anaesthetised intraperitoneally with ketamine (40 mg/kg; Ketalar, Pfizer) and xylazine hydrochloride (4 mg/kg; Alfazyne 1, Ege Vet, Alfasan International BV). After the subjects were placed in a prone position, ECG recordings were taken from the D2 lead with needle electrodes (Fig. 1B). ECG recordings were evaluated with the Biopac MP36 system. RR and QT intervals and heart rates (HR) were measured by ECG recordings at baseline, and at the first and second hour, respectively. Heart rate was calculated as 1 500 per number of small squares between consecutive R waves. After the QT interval and HR measurements were performed, the corrected QT (QTc) was calculated with the Bazzet formula ($QT/RR^{1/2}$).

QTc prolongation, measured by serial ECG, was the accepted main endpoint. In a similar previous experimental model, researchers showed that the QTc difference of rats two hours after drug administration was 43 ms between the control and amitriptyline groups.[12] It is generally accepted that a 20-ms change in QTc interval is significant.[13] Therefore, in order to detect a difference of 20 ms in QTc interval between the groups, six rats per group would be required for a total of 24 rats to be able to reject the null hypothesis with a probability (power) of 0.8. The type I error probability associated with this test of the null hypothesis was 0.05.

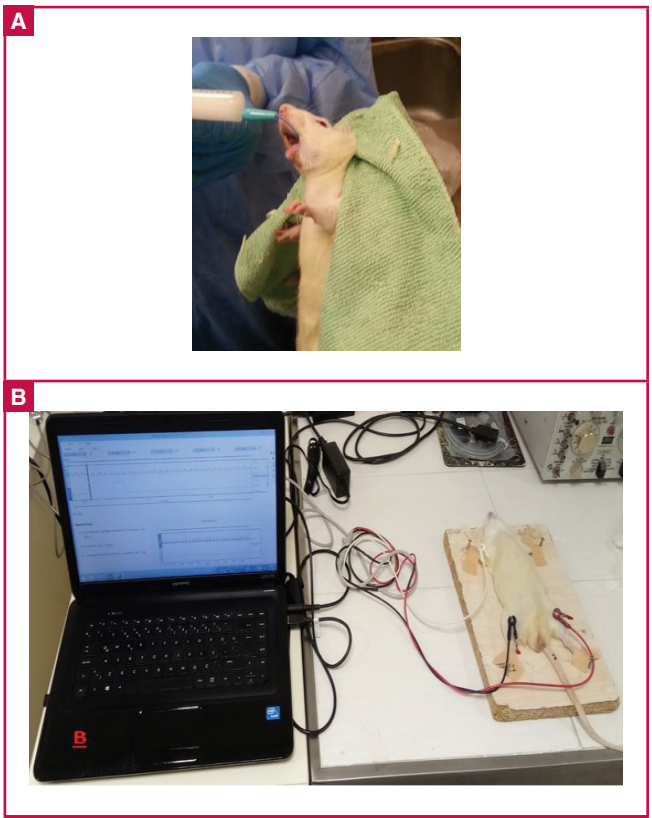

Fig. 1. A. Drug administration to the animals via an oral tube. B. ECG recording of the rats from the D2 lead in a supine position with the Biopac MP36 system.

Statistical analysis

Statistical analyses were performed with SPSS 22 (IBM Corp, Armonk, NY, USA). The mean and median QT, HR and QTc durations of all groups were calculated. The Shapiro–Wilk test was used to evaluate whether the data fitted a normal distribution. All ECG parameters at all available time points (baseline, first and second hours) were compared with repeated measurements of one-way analysis of variance (ANOVA), followed by Tukey's or Tamhane *post hoc* tests. ECG parameters of all of the study groups at each time point (baseline, first and second hours) were also separately compared.

Data without a normal distribution are expressed as median and interquartile range (IQR) and were compared by Kruskal–Wallis analysis (HR at first hour). Data with a normal distribution are expressed as mean ± standard deviation (SD) and were compared using ANOVA, followed by Tukey's test for *post hoc* analysis (for other parameters). Differences of $p < 0.05$ were considered significant.

Results

After anaesthesia, ECG recordings of the four groups at baseline, and first and second hours were obtained and compared between all groups (Table 1). The measurements of the control group were within normal limits and consistent with the literature.[13] In the control group, QT was 77.33 ± 9.02 ms at baseline, 73.50 ± 2.26 ms at the first hour, and 78.17 ± 6.18 ms at the second hour. The QTc calculation was 165.42 ± 18.34 ms at baseline, 166.63 ± 17.92 ms at the first hour, 184.65 ± 12.86 ms at the second hour (Table 1). ECG findings of the EMPA group were within normal limits and similar to the control group (Table 1). Although baseline HR were different between the groups, after anaesthesia all HR became similar and consistent with the literature (Table 1).

The durations of QT interval and QTc were found to be statistically longer in the AMT group than in the control group at the first and second hours ($p \leq 0.001$) (Table 1, Fig. 2). EMPA significantly ameliorated AMT-induced QT and QTc prolongation. The durations of the QT interval were significantly lower at the first ($p < 0.001$) and second hours ($p < 0.01$) in the AMT+EMPA group compared to the AMT group. Moreover, the QTc calculation was significantly lower in the AMT+EMP group than in the AMT group at the first and second hours ($p < 0.01$) (Table 1).

ECG comparisons of all groups for one second within the second hour can be seen in Fig. 3. When the changes in baseline, and first and second hours of the QT intervals of the groups were compared with repeated measurements ANOVA, there was a significant difference between time points ($p < 0.001$). Moreover,

Table 1. QT, QTc durations and heart rate for all groups at basal, first and second hour

Variables	*Control*	*Empagliflozin*	*Amitriptilin*	*Amitriptilin + empagliflozin*	p-*value*
Baseline					
Qt (ms), mean ± SD	77.33 ± 9.02	78.33 ± 6.28	71.50 ± 5.68	73.33 ± 8.02	0.35
QTc (ms), mean ± SD	165.42 ±18.34	152.57± 11.07	163.11 ± 11.59	159.97 ±15.18	0.453
HR, mean ± SD	263.00 ± 39.38	230.00 ± 10.06	314.83 ± 42.48	287.50 ± 29.99	0.002
First hour					
Qt (ms), mean ± SD	73.50 ± 2.26	75.67 ± 4.27	108.67 ± 5.96[A]	90.33 ±5.39[B]	< 0.001
QTc (ms), mean ± SD	166.63 ± 17.92	154.60 ± 20.43	227.45 ± 26.89[A]	179.40 ±17.63[C]	< 0.001
HR, median (IQR)	335.50 (75.75)	245.00 (144.25)	248.50 (123.50)	232.50 (107.25)	0.279
Second hour					
Qt (ms), mean ± SD	78.17 ± 6.18	77.33 ± 7.31	106.00 ± 12.60[A]	87.83 ± 4.54[C]	< 0.001
QTc (ms), mean ± SD	184.65 ± 12.86	171.63 ± 20.36	229.89 ± 19.83[D]	191.66 ± 10.93[C]	< 0.001
HR, mean ± SD	335.83 ± 21.99	295.67 ± 30.54	288.67 ± 53.86	326.30 ± 36.97	0.118

[A]amitiriptilin vs control < 0.001
[B]amitriptilin + empagliflozin vs amitriptilin < 0.001
[C]amitriptilin + empagliflozin vs amitriptilin < 0.01
[D]empagliflozin vs amitriptilin: 0.001.

there was a significant difference between the AMT group and all the other groups ($p < 0.01$). In addition, when the changes in baseline, and first and second hours of the QTc intervals of the groups were compared with repeated measurements ANOVA, there was a significant difference between time points ($p < 0.001$). There was also a significant difference between the AMT group and all the other groups ($p < 0.001$ for AMT vs control and EMPA groups, $p < 0.01$ for AMT vs AMT+EMPA).

Discussion

In this study, we investigated the effects on QT interval of the concomitant use of EMPA and AMT, which have different effects on Na and Ca metabolism in cardiomyocytes, and it was found that EMPA significantly inhibited AMT-induced QT prolongation. AMT-induced QT and QTc interval prolongations were measured in the first and second hours by ECG recording, and it was determined that EMPA significantly ameliorated these prolongations.

EMPA exerts its antidiabetic effect by decreasing glucose absorption in the kidney proximal tubule as a result of its inhibitory activity in SGLT-2 channel.[1] In the EMPA-REG OUTCOME clinical study, in addition to the antidiabetic effect of EMPA, it was shown that EMPA reduced all-cause mortality (including cardiovascular death) and hospitalisations caused by heart failure.[2] Moreover, it was shown that EMPA reduced cardiovascular death and hospitalisation for heart failure in heart failure patients with or without diabetes mellitus. EMPA did not cause hypoglycaemia in patients without diabetes in the EMPEROR-Reduced trial.[14] However, physiopathological explanation of this beneficial effect of EMPA on reducing cardiovascular mortality has not been fully achieved.

In the literature, clinical studies revealed that EMPA reduced arterial stiffness, cardiac oxygen demand and albuminuria. Animal studies have shown that EMPA regressed left ventricular fibrosis/remodelling and it had positive effects on left ventricular systolic and diastolic function.[15-22] Also, in cellular studies conducted with diabetes models, it has been shown that EMPA reduced the amount of cytosolic Na in myocytes by inhibiting

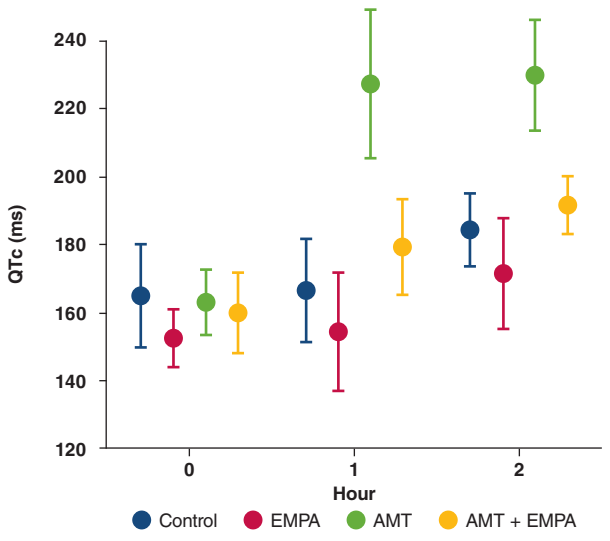

Fig. 2. QTc comparisons for all groups at the basal, first and second hours.

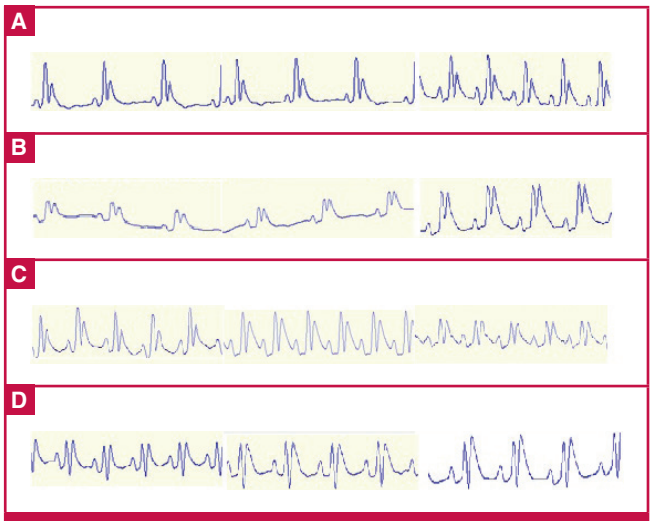

Fig. 3. ECG comparisons of all groups at basal, first and second hour. A. control, B. EMPA group, C. AMT group, D. AMT+EMPA group.

the sodium hydrogen exchanger (NHE).[3] EMPA was also effective in intracellular Ca balance by increasing the L-type Ca channel activity, the amount of sarcoplasmic reticulum ATPase (SERCA2a) protein and the levels of ryanodine receptor-2,[4] regardless of its SGLT-2 inhibition.

AMT is a TCA drug that can be used in many indications, such as anxiety, depression and diabetic neuropathy. In addition to the wide clinical uses of TCA, the cardiotoxicity caused by the use of these drugs limits the use of all TCAs, primarily AMT.[6] AMT may cause cardiotoxicity due to ventricular arrhythmias caused by the prolongation of the QRS, QTc and PR segments, as seen on ECG, as a result of Na channel inhibition caused by AMT.[7] Since the cardiotoxicity caused by AMT is not dose dependent, it is important to monitor the ECG findings.[23] In our study, we found that EMPA significantly prevented AMT-induced QTc prolongation. This protective effect can be explained by reviewing the effects of these two drugs on cellular Na and Ca balances.

In the established medical literature, it has been reported that AMT and other TCAs cause cardiotoxicity, mainly by Na channel blockage.[24] In the toxicity of AMT, QRS prolongation, right bundle branch block mimicking Brugada pattern or PR segment prolongation can be observed on ECG due to Na channel inhibition.[25] However, Na channel inhibition cannot explain QTc prolongation in the toxicity of AMT.

Actually, it is known that Na channel activation, in contrast to its inhibition, may lead to long QT. The *SCN5a* gene encodes the fast Na channels activated in phase 0 of the cardiac action potential, and congenital long QT syndrome is observed in *SCN5a* gene mutants, increasing the activity of this channel.[16] In the treatment of this condition, quinidine[26] and ranolazine,[27] which indicate their activities with Na channel inhibition, are effective and are recommended in the guidelines.[28] Therefore, it is insufficient to explain this situation only with QTc prolongation caused by Na channel inhibition.

In fact, in a study by Baartscheer *et al*., it has been shown that EMPA reduces the amount of cytosolic Na during systole by inhibiting the NHE activity in myocytes.[3] If this effect of EMPA is considered together with the Na channel blockade caused by AMT, it would be expected that EMPA extends QT prolongation further, instead of its effect on preventing QT prolongation in AMT toxicity.

In a study by Aleksey *et al*., it has been shown that there are crucial cellular mechanisms in which AMT cardiotoxicity can occur with intracellular Ca metabolism.[8] In this study, it was shown that the toxic dose of AMT increased the amount of sarcoplasmic Ca and the Ca permeability of ryanodine channels, and decreased SERCA-mediated Ca re-uptake by decreasing the Ca binding capacity of calsequestrin. The toxic dose of AMT may lead to cardiotoxicity by increasing Ca release during systole via the sarcoplasmic reticulum as a result of this.[8]

In a study by Lee *et al*., it was shown that EMPA increased Ca re-uptake by causing a significant increase in SERCA activity, and decreased Ca sparks by causing inhibition of ryanodine activity.[4] Also, in this study, it was found on ECG that EMPA had anti-arrhythmic effects against QT prolongation by both reducing reactive oxygen species (ROS) activity and shortening action potential duration.[4] Our previous findings have also shown that EMPA can prevent QTc prolongation, induced by sotalol, in an *in vivo* animal study.[29] In our study, we believe that the beneficial effects of EMPA on AMT-induced QT prolongation originates from these pathways affecting intracellular Ca homeostasis.

In the literature, there are many studies on the cardiotoxicity of AMT. In a study by Akgun *et al*., it was shown that glucagon had beneficial effects on hypotension and QRS prolongation caused by AMT.[30] It was observed that theophylline and adenosine receptor antagonists ameliorated the AMT-induced QRS prolongation.[31,32] However, there are very few studies on QT prolongation, which is the most important indicator of AMT toxicity seen on ECG.

In a study by Basol *et al*., it was stated that edaravone, a potent antioxidant, ameliorated the AMT-induced QT prolongation.[33] In this study, while the possible physiopathological and cellular mechanisms of this improvement in QT prolongation were not included, it was shown that edaravone leads to a decrease in the retention of technetium pyrophosphate and an increase in cardiac troponin levels, as a result of myocardial damage caused by AMT. Also in this study, it was concluded that AMT caused cardiotoxicity by increasing ROS activity, and edaravone ameliorated this situation.[33]

In another study by Basol *et al*., the effects of diltiazem and metoprolol in QT prolongation due to AMT was investigated. In this study, it was shown that both molecules (diltiazem and metoprolol) had beneficial effects against QT prolongation due to AMT. It was interpreted that this effect may be due to both molecules reducing the amount of cytosolic Ca in phase 2 of the cardiac action potential.[12] In addition, in the EMPEROR-Preserved trial, the beneficial effect of EMPA in patients with heart failure with preserved ejection fraction may also be due to its preventative effects on intracellular Ca accumulation, which was also shown in our study.[34]

Limitations

In this study, the positive effects of EMPA on AMT-induced QT prolongation were basically attributed to intracellular Ca balance. However, since this study did not include cellular biophysics research, this opinion remains a hypothesis. In addition, the study was only an ECG study, other markers such as troponin and scintigraphy, which may show AMT-induced cardiotoxicity, were not used in this study.

Conclusion

The preventative effects of EMPA on the QT and QTc prolongation due to AMT, a tricyclic antidepressant, have been shown in our study. According to our research, this is the first study to show this benefit of EMPA, which can prevent AMT cardiotoxicity. We attribute these effects to the opposite effects of both molecules in the intracellular Ca balance. From the results of this study, it can be deduced that it is beneficial to use EMPA as an antidiabetic agent to prevent QT and QTc prolongation and concurrent arrhythmic events in diabetic patients with cardiovascular diseases when AMT is prescribed. In addition to these basic animal experiments, clinical research is needed to confirm this effect. Moreover, this study shows how EMPA could be beneficial in patients with heart failure with preserved ejection fraction.

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