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Is sofosbuvir/ledipasvir safe for the hearts of children with hepatitis C virus?

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ABSTRACT

Background: Symptomatic bradycardia has been reported in adults treated for chronic hepatitis C using sofosbuvir based regimens.
Aim: We studied the cardiac safety of sofosbuvir/ledipasvir in Egyptian children, treated for chronic hepatitis C.
Methods: The study included 40 hepatitis C virus infected children and adolescents 12–17 years old, using the combination of sofosbuvir (400 mg)/ledipasvir (90 mg) in a single oral tablet (Harvoni) taken daily for 12 weeks. All subjects underwent a baseline standard 12-lead surface Electrocardiography that was repeated at 4 and 12 weeks of therapy. Electrocardiography parameters (Heart Rate, RR interval, PR interval, QRS, QT interval, corrected QT interval, QT dispersion, JT interval, corrected JT interval, JT dispersion, Tpeak-Tend interval) were compared at the 3 different time points during antiviral therapy.
Results: No symptoms related to the cardiovascular system were reported during treatment. There were no cases of symptomatic bradycardia/syncope. Heart rate was noted to be significantly lower and RR and QT intervals were significantly longer in the baseline electrocardiography. Heart rate was significantly lower and RR interval was significantly longer in patients with higher viral load.
Conclusion: No adverse cardiovascular events were observed in this group of HCV infected children and adolescents treated with sofosbuvir/ledipasvir. None of the patients developed bradyarrhythmias during treatment.

1. Introduction

Hepatitis C virus (HCV) infection in Egypt was reported as the highest prevalence in the world [1–3]. The most common HCV genotype in Egypt is genotype 4 (GT4) [4]. Treatment of chronic hepatitis C (CHC) slows disease progression, prevents complications of cirrhosis, reduces the risk of hepatocellular carcinoma and extrahepatic complications of the virus [5]. Combination of pegylated interferon (PEG IFN)-α2b and ribavirin (RBV) was approved by the Food and Drug Administration (FDA) in December 2008 and by the European Medicines Agency in December 2009 for treatment of children aged 3 years and older [6]. IFN-based regimens have numerous side effects, which have a negative influence on tolerability and adherence of patients to treatment [7]. HCV treatment in children using combination of PEG IFN-α2b and RBV for 48 weeks resulted in a 42.4% sustained virological response 24 weeks after end of treatment (SVR24) with numerous adverse effects including fever in 90% and neutropenia in more than 50% [8].

Since 2015, reports on the use of the direct acting antiviral agents (DAAs), a polymerase inhibitor such as sofosbuvir (SOF), to treat HCV showed high SVR rates [9]. In combination with other nonstructural 5A protein or protease inhibitors (such as ledipasvir [LED]), SOF-based regimens have demonstrated more than 90% SVR in patients with CHC, with much lower rates of serious side effects of less than 5% [10], resulting in good tolerability [11].

The most reported side effects occurring in 10% of patients receiving SOF/LED are headaches and fatigue; while rashes, nausea, diarrhea, and insomnia occur less commonly (1%–10%) [10]. Despite no major cardiovascular safety concerns with SOF in several, large-scale clinical trials [12], some case reports have recently demonstrated its possible role in cardiac bradyarrhythmias, mostly in adult patients on amiodarone; the mechanism of which is yet to be established [13,14].

To date, reports on the effects of SOF/LED on cardiac rhythm in children are lacking. Accordingly, in this work we aimed to study

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the effect of SOF/LED on electrocardiographic (ECG) changes in Egyptian children aged 12–17 years treated for CHC.

2. Patients and methods

2.1. Study design and setting

This prospective observational single-center study was carried out at the Pediatric Hepatology Unit, Cairo University Pediatric Hospital, Egypt. Following the FDA approval of the first DAAs for HCV in children in April 2017, we started in July 2017 to treat children 12–17 years old of both sexes using the combination of SOF (400 mg) plus LED (90 mg) in a single oral tablet taken daily for 12 weeks. The study protocol was approved by the institutional review board. This study was conducted in full accordance with the principles of the 1976 Declaration of Helsinki and its later amendments. A written informed consent was signed by the parents/guardians before starting treatment after explaining the treatment plan and possible risks. This study was approved by the Ethics Committee of the Departments of Pediatrics, Kasr Alainy School of Medicine, Cairo University, Cairo, Egypt.

2.2. Participants

The study included 40 children and adolescents of both sexes, aged 12–17 years, infected with HCV for at least 6 months, both treatment-naive and treatment-experienced. Patients were diagnosed as chronically infected with HCV based upon presence of antibodies to HCV and positive HCV RNA for more than 6 months. All cases had normal estimated glomerular filtration rate and normal basal heart rate (HR). Patients co-infected with hepatitis B virus (HBV) were excluded.

2.3. Data collection

2.3.1. Pre-enrollment data collection included:

- Full clinical examination.
- Careful review of prior medications and changes or modifications were done as clinically indicated in cases of possible or likely interaction with DAAs [9].
- Investigations: complete blood count, liver function tests [total and direct serum bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), gamma glutamyl transpeptidase (GGT), serum albumin, and prothrombin time (PT)], hepatitis B surface antigen (HBsAg), serum creatinine and HCV RNA quantitation.

HCV-RNA testing was performed using quantitative real-time polymerase chain reaction (PCR) on Applied Biosystems 7500 Real time PCR System using kits supplied by Qiagen [Qiagen GmbH (Hoffmann-La Roche AG), Hilden, Germany].

- Transient elastography for fibrosis staging using a FibroScan device (FibroScan Echosens, Paris, France).
- Twelve-lead ECGs were recorded with the same device (Schiller, AT 60, Baar, Switzerland) with patients in the supine position and breathing freely, after 1 min of resting.

Electrocardiographic Measurements: All subjects underwent a standard 12-lead surface ECG recorded at a paper speed of 25 mm/s and gain of 10 mm/mV. All ECG recordings were done in the morning between 9 and 11 am to avoid diurnal variations. Tracings were analyzed by a single investigator blinded to patient clinical data. All ECG parameter measurements (HR, RR interval, PR interval, QRS, QT interval, corrected QT interval [QTc], QT dispersion [QTd], JT interval, corrected JT interval [JTc], JT dispersion [JTd], Tpeak-Tend [Tp-e] interval) were manually performed. For each lead, the analysis included at least 3 consecutive heart cycles. The previously mentioned ECG parameters were analyzed as measures of altered ventricular repolarization which is associated with a high risk of ventricular arrhythmias [15–18].

- The QRS duration was measured from the start of the Q wave or, in its absence, from the start of the R wave to the end of the S wave i.e. its return to the isoelectric line.
- The QT interval was measured (in leads II or V5) from the initial deflection of the QRS complex to the end of the T wave (the end of the T wave: the intercept between the isoelectric line with the tangent drawn through the maximum down slope of the T wave).
- The JT interval was derived by subtracting QRS duration from QT interval.
- QTd and JTd were defined as the difference between the longest and shortest QT and JT intervals respectively.
- QTc and JTc were performed with the Bazett's formula [19].
- The Tp-e interval was defined as the interval from the maximum T-wave amplitude to the end of the T-wave in the precordial lead V5 (or in leads V4 and V6 if not measurable in V5).
- Tp-e/QTc ratio was calculated.

2.3.2. Follow up data collection included:

- Medication side effects were recorded through a questionnaire answered by the patients at weeks 4, 8 and 12; including: jaundice, asthenia, fatigue, headache, cough, nausea, diarrhea, insomnia, irritability and skin rash. Special emphasis was paid to symptoms related to the cardiovascular system including: palpitations, dizziness, syncope, chest pain or dyspnea.
- Investigations: complete blood count, full liver function tests, serum creatinine and HCV RNA quantitation were repeated on weeks 4, 8, 12 of therapy and 12 (SVR 12) and 24 weeks (SVR 24) after end of therapy.
- ECG tracings were repeated at 4 and 12 weeks of therapy.

2.4. Statistical methods

Data were analyzed using the software, Statistical Package for Social Science (SPSS Inc. Released 2009, PASW Statistics for Windows, version 18.0: SPSS Inc., Chicago, Illinois, USA). Mean and standard deviation (SD) or median and interquartile range (IQR) were estimates of quantitative data including age, laboratory results and ECG changes; while frequency and percentage were estimates of qualitative data as sex, clinical data and fibrosis staging. Comparison between ECG parameters at baseline versus week 4 and week 12 of therapy was done as well as comparison between baseline ECG parameters in treatment-naive patients and those previously treated with IFN. Differences were tested by Student's paired t-test. P values of less than 0.05 were considered significant.

3. Results

Baseline parameters of the study subjects are shown in Table 1. None of the patients experienced symptoms related to the cardiovascular system in the form of palpitations, dizziness, syncope, chest pain or dyspnea before or during treatment.

The aforementioned ECG parameters were analyzed and compared at 3 time points: at baseline and 4 and 12 weeks after start of treatment. The HR, RR interval, QT interval were within normal ranges throughout the study; however the HR was noted to be significantly lower in the initial ECG (prior to treatment) compared to the ECGs done at 4 and 12 weeks of therapy (Table 2). RR intervals and QT intervals were also found to be significantly longer in

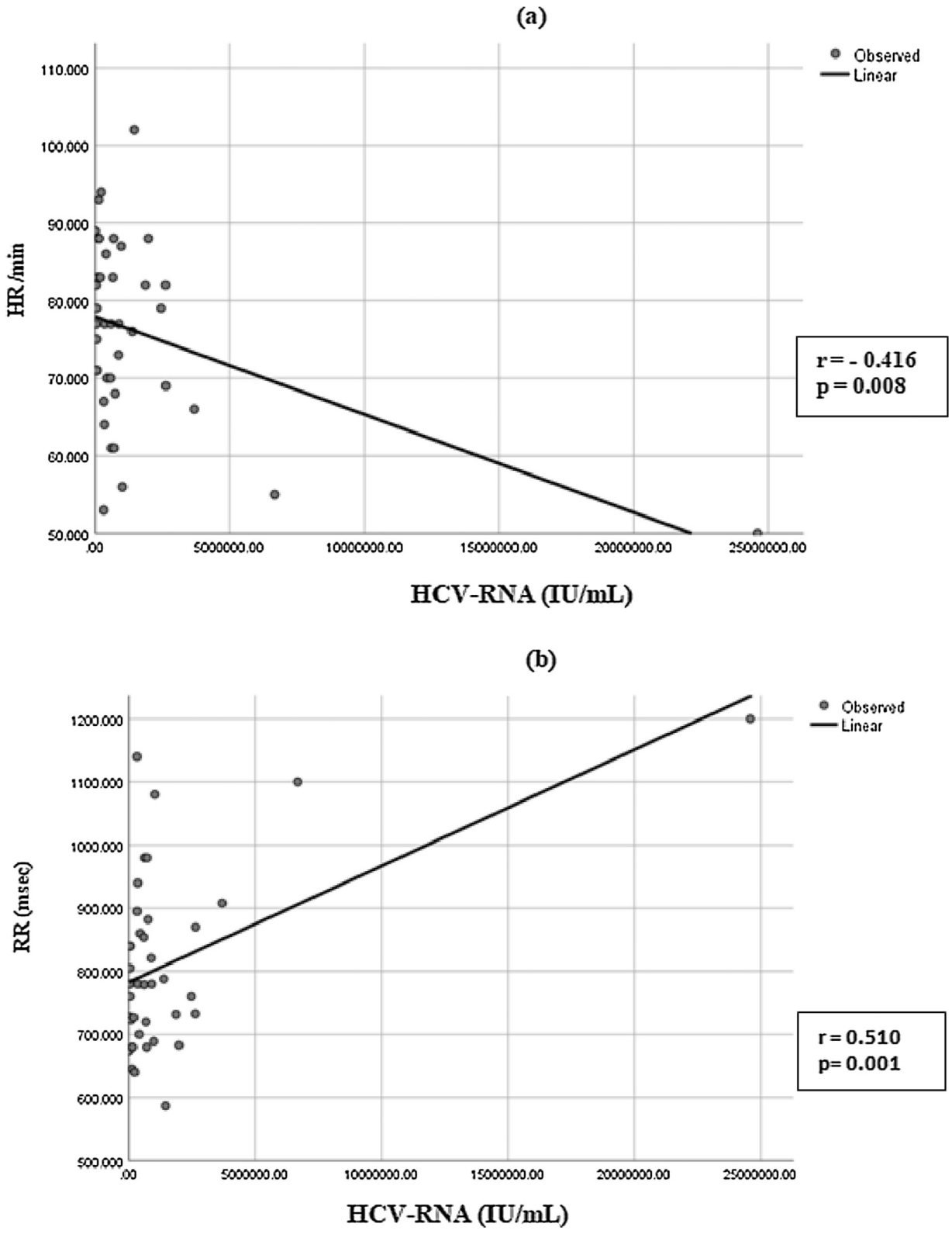

Fig. 1. Correlations between viral load and (a) basal heart rate and (b) basal RR intervals of ECG.

the baseline ECGs as compared to weeks 4 and 12 of treatment (Table 2). The baseline HR was significantly lower (Fig. 1a) and RR interval was significantly longer (Fig. 1b) in patients with higher viral load. Furthermore, when we compared the baseline ECGs of treatment-naive patients with those who were previously treated with IFN, only the QT duration was significantly longer in those who previously received IFN (Table 3).

QTc intervals were mostly within normal range (404.6 ± 27.4 ms initially, 400.8 ± 26.5 and 403.05 ± 23.5 ms at 4 and 12 weeks respectively) with no significant changes over the treatment period (Table 2). Although QTd was higher in initial ECGs, there were no statistically significant differences from the second and third ECGs.

Table 1
Baseline data of 40 studied children and adolescents infected with HCV.

Variables		Range (min–max)
Age in years; mean ± SD	13.950 ± 1.53	11.5–17
Sex, n (%)		
Male	24 (60)	
Female	16 (40)	
Liver function tests; median (IQR)		
Total bilirubin; mg/dL	0.4 (0.3)	0.1–2.1
ALT; IU/L	68 (50)	11–226
AST; IU/L	51 (40.25)	24–209
AP; IU/L	221 (156.75)	18–596
GGT; IU/L	46.5 (67.7)	11–435
Albumin; gm/dL; mean + SD	4.1 ± 0.5	2.5–4.9
INR; mean + SD	1.1 ± 0.08	1–1.2
HCV-RNA (IU/mL), median (IQR)	587000 (1154500)	9630–24600000
Transient elastography, ± liver biopsy; n (%)		
Fibrosis stage F0 and F0-1	32 (80%)	
Fibrosis stage F1–F2	2 (5%)	
Fibrosis stage F3	4 (10%)	
Fibrosis stage F4–5	2 (5%)	

ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; GGT = gamma glutamyl transpeptidase; HCV = hepatitis C virus; IQR = interquartile range; SD = standard deviation.

Twelve patients had long JTc (>340 ms) in their initial ECG, compared to 11 and 14 patients in the follow up ECGs, while the JTd was increased (>40 ms) in 2, 5 and 4 patients in their initial and follow up ECGs respectively. However, both parameters did not show significant changes over the treatment period (Table 2).

Other ventricular repolarization parameters: Tp-e/QT was prolonged (>0.24), in 3 patients initially as compared to 2 and 3 patients in the second and third follow up ECGs respectively. Tp-e and Tp-e/QTc were noted to be significantly higher in the initial ECG compared to the ECGs done at 4 and 12 weeks of therapy (Table 2), while Tp-e/QT was significantly lower at 12 weeks ECG as compared to 0 and 4 weeks. However, there was no significant correlation between such parameters and the viral load or the degree of fibrosis by transient elastography.

The QRS duration was normal throughout the study period in all patients except one patient who had persistently wide QRS complex with right bundle branch block (BBB) (he had prior cardiac surgery for repair of tetralogy of Fallot).

The QTc interval was borderline-long (462 ms) in one patient in the initial ECG, however the follow up ECGs showed normal QTc (409 and 423 ms respectively). This patient was known to have a complex congenital heart disease with previous two cardiac surgeries (Glenn anastomosis and Fontan operation). Her ECG also showed left BBB. Other clinically insignificant ECG findings (incomplete right BBB in 2 patients, biventricular hypertrophy criteria in 3 patients and right ventricular hypertrophy criteria in 2 patients) were noted and echocardiography was done in all those patients and was found normal.

4. Discussion

The results of this study show that, the combination of SOF (400 mg) plus LED (90 mg) in a single oral tablet (Harvoni) used in the treatment of HCV infection in children and adolescents 12–17 years of age did not induce adverse changes in the ventricular repolarization potentially associated with clinically significant arrhythmias. No significant changes in the PR duration, or QRS duration were observed, in addition to the absence of severe bradycardia, sinus node dysfunction, or atrio-ventricular block.

Fontaine et al. reported serious brady-arrhythmias associated with SOF treatment that occurred with amiodarone co-administration [14]. While Durante-Mangoni et al. reported that in the absence of amiodarone co-administration, none of the current DAA regimens induces serious changes in cardiac electrical activity [20].

Although the QT interval was significantly lower after 4 and 12 weeks of therapy, treatment did not influence QTc interval, QTd and JTc interval. Indeed, QTc and JT intervals, as well as QTd and JTd, remained within the normal range during the 12 treatment weeks. Tp-e, Tp-e/QT and Tp-e/QTc were noted to be significantly lower in the ECGs done during therapy compared to the baseline ECG. Thus, the net effect of SOF on ventricular repolarization in the present work was either insignificant change or effects denoting an even reduced risk of ventricular tachyarrhythmia. This may be attributable to HCV elimination. Matsumori et al., reported that frequencies of atrial and ventricular arrhythmias were increased in HCV patients than controls [21].

QT prolongation has long been reported as one of the most important cardiac alterations related to cirrhosis [22], with a strong relationship between severity of cirrhosis and ECG findings of cirrhotic cardiomyopathy [23–26]. QTc prolongation and QTd were even noted to decrease after liver transplantation [27]. To be noted, our patients were children and adolescents, and HCV is not expected to lead to cirrhosis in this age group. Transient elastography demonstrated F0–F1 in 80% of patients. Pediatric HCV may only tend to lead to cirrhosis later in life [28]. A study of 121 children with CHC and a mean age of 10 years found that cirrhosis was only present in 2% of the sample [29].

To our knowledge, this is the first work studying the electrocardiovascular effects of SOF/LED in children and adolescents with CHC infection. The results of this study are comparable to what Durante-Mangoni et al., reported in their series of adults with CHC [20]. They

Table 2
Comparison between ECG parameters at baseline versus week 4 and week 12 of therapy.

ECG variables	Baseline	Week 4 of therapy	Week 12 of therapy	P-value 1 0 vs. 4	P-value 2 0 vs. 12	P-value 3 4 vs. 12
RR in ms; mean ± SD	811.07 ±142.5	731.67 ± 54.46	739.2 ± 107.29	**0.002**	**0.000**	0.738
HR/min; mean ± SD	76 ±11.9	82 ± 12.39	82.7 ± 11.4	**0.000**	**0.000**	0.597
QRS duration in ms; mean ± SD	76.6 ±17.75	76.6 ± 15.12	73.45 ± 14.4	0.991	0.222	0.086
PR duration in ms; mean ± SD	136.2 ±17.2	157.5 ± 111.9	137.2 ± 16.6	0.245	0.655	0.263
QT duration in ms; mean ± SD	361.9 ± 25.37	345.8 ± 23.49	344.9 ± 21.6	**0.000**	**0.000**	0.741
QT max in ms; mean ± SD	377.7 ± 23.51	360.05 ± 23.6	359.9 ± 23.3	**0.000**	**0.000**	0.962
QT min in ms; mean ± SD	345.9 ± 23.75	330.4 ± 24.9	331.1 ± 21.5	**0.000**	**0.000**	0.832
QTc duration in ms; mean ± SD	404.6 ± 27.4	400.8 ± 26.5	403.05 ± 23.5	0.445	0.689	0.516
QTd in ms; mean ± SD	32.5 ± 10	32.9 ± 11.6	29.3 ± 12.13	0.872	0.209	0.220
JTc duration in ms; mean ± SD	328.27 ± 34.06	325.5 ± 30.9	332.17 ± 35.7	0.569	0.439	0.105
JTd in ms; mean ± SD	27.6 ± 10	29.7 ± 11.4	26.5 ± 11.7	0.355	0.654	0.259
Tp-e in ms; mean ± SD	73 ± 9.3	69.1 ± 11.6	63.9 ± 12.13	**0.037**	**0.000**	**0.020**
Tp-e/QT; mean ± SD	0.2058 ± 0.028	0.2005 ± 0.0327	0.185 ± 0.035	0.437	**0.009**	**0.029**
Tp-e/QTc; mean ± SD	0.1832 ± 0.0265	0.1714 ± 0.0329	0.1589 ± 0.030	**0.048**	**0.000**	**0.035**

ECG = electrocardiogram; HR = heart rate; JTc = corrected JT; JTd = JT dispersion; QTc = corrected QT interval; QTd = QT dispersion; SD = standard deviation; Tp-e = Tpeak-Tend.

Table 3
Comparison between treatment-naive patients and treatment-experienced patients as regards baseline ECG parameters.

Baseline ECG variables	Treatment-naive patients (n = 30)	Treatment-experienced patients (n = 10)	P value
RR in ms; mean ± SD	791.53 ± 145.01	869.7 ± 123.5	0.135
HR/min; mean ± SD	77.9 ± 12.09	70.3 ± 10.1	0.082
QRS duration in ms; mean ± SD	75.13 ± 15.8	81.2 ± 23	0.356
PR duration in ms; mean ± SD	135.26 ± 16.6	139.1 ± 19.5	0.549
QT duration in ms; mean ± SD	355.8 ± 20.09	380.4 ± 31.3	**0.006**
QT max in ms; mean ± SD	373.73 ± 21.8	389.6 ± 25.5	0.064
QT min in ms; mean ± SD	341.46 ± 19.5	359.2 ± 30.7	**0.039**
QTc duration in ms; mean ± SD	402.93 ± 25.69	409.6 ± 33	0.513
QTd in ms; mean ± SD	31.6 ± 9.1	35.4 ± 12.58	0.308
JTc duration in ms; mean ± SD	328.26 ± 30.3	328.3 ± 45.4	0.998
JTd in ms; mean ± SD	27.63 ± 9.16	27.8 ± 12.7	0.964
Tp-e in ms; mean ± SD	73.86 ± 8.2	74.4 ± 12.8	0.879
Tp-e/QT; mean ± SD	0.208 ± 0.025	0.198 ± 0.034	0.309
Tp-e/QTc; mean ± SD	0.183 ± 0.025	0.182 ± 0.0298	0.845

ECG = electrocardiogram; HR = heart rate; IFN = interferon; JTc = corrected JT; JTd = JT dispersion; QTc = corrected QT interval; QTd = QT dispersion; SD = standard deviation; Tp-e = Tpeak-Tend.

reported that despite a transient increase of QTc duration during the first week of therapy, however, with continuing SOF use, the QTc duration returned to baseline values, whereas QTd decreased during the whole observation period; whereas JT dispersion also decreased up to week 2. Our findings are consistent with those of previous safety studies, showing that SOF did not prolong QTc to any clinically relevant extent as per the manufacturer [30].

The study limitations include the use of a single method to assess changes in cardiac electrical activity, namely 12-lead surface ECG and the relative limited patient number. However, this number of HCV infected children with GT4 and assessment of ECG tracings at different time points (baseline, during and after end of treatment) were the major strengths of our study design.

5. Conclusion

In conclusion, SOF/LED was found to be safe with no adverse cardiovascular events observed in our group of HCV infected children and adolescents treated for CHC. None of the patients developed bradyarrhythmias during treatment.

Conflict of interest

None declared.

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