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ORIGINAL ARTICLE

Dynamics of the QTc interval over a 24-h dose interval after start of intravenous ciprofloxacin or low-dose erythromycin administration in ICU patients

Florine A. Berger[1] | Willem van Weteringen[2] | Heleen van der Sijs[1] | Nicole G. M. Hunfeld[1,3] | Jeroen J. H. Bunge[3,4] | Natasja M. S. de Groot[4] | Patricia M. L. A. van den Bemt[1,5] | Teun van Gelder[1,6]

[1]Department of Hospital Pharmacy, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands

[2]Department of Paediatric Surgery, Erasmus MC Sophia Children's Hospital, University Medical Center Rotterdam, Rotterdam, the Netherlands

[3]Department of Intensive Care, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands

[4]Department of Cardiology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands

[5]Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Groningen, the Netherlands

[6]Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, the Netherlands

Correspondence
Florine A. Berger, Department of Hospital Pharmacy, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands.
Email: f.berger@erasmusmc.nl

Abstract

QTc interval prolongation is an adverse effect associated with the use of fluoroquinolones and macrolides. Ciprofloxacin and erythromycin are both frequently prescribed QTc-prolonging drugs in critically ill patients. Critically ill patients may be more vulnerable to developing QTc prolongation, as several risk factors can be present at the same time. Therefore, it is important to know the QTc-prolonging potential of these drugs in the intensive care unit (ICU) population. The aim of this study was to assess the dynamics of the QTc interval over a 24-hour dose interval during intravenous ciprofloxacin and low-dose erythromycin treatment. Therefore, an observational study was performed in ICU patients (≥18 years) receiving ciprofloxacin 400 mg t.i.d. or erythromycin 100 mg b.i.d. intravenously. Continuous ECG data were collected from 2 h before to 24 h after the first administration. QT-analyses were performed using high-end holter software. The effect was determined with a two-sample *t*-test for clustered data on all QTc values. A linear mixed model by maximum likelihood was applied, for which QTc values were assessed for the available time intervals and therapy. No evident effect over time on therapy with ciprofloxacin and erythromycin was observed on QTc time. There was no significant difference ($p = 0.22$) in QTc values between the ciprofloxacin group (mean 393 ms) and ciprofloxacin control group (mean 386 ms). The erythromycin group (mean 405 ms) and erythromycin control group (mean 404 ms) neither showed a significant difference ($p = 0.80$). In 0.6% of the registrations (1.138 out of 198.270 samples) the duration of the QTc interval was longer than 500 ms. The index groups showed slightly more recorded QTc intervals over 500 ms. To conclude, this study could not identify differences in the QTc interval between the treatments analyzed.

The authors confirm that the Principal Investigator for this paper is prof. Dr. P.M.L.A. van den Bemt and that she had direct clinical responsibility for patients.

KEYWORDS
arrhythmia, ciprofloxacin, drug interactions, erythromycin, ICU, QTc prolongation

1 | INTRODUCTION

To date, 60 drugs are known for their QTc-prolonging effects with a known risk of Torsade de Pointes (TdP), a rare, but potentially fatal ventricular tachycardia.[1] According to the European Medicine Agency (EMA) guidelines, a QTc interval is prolonged when it exceeds 450 ms in males and 470 ms in females. A QTc interval of >500 ms or an increase of 60 ms or more from baseline is associated with a higher occurrence of TdP and is, therefore, considered to be clinically relevant. When two or more QTc-prolonging drugs are prescribed, medication surveillance in terms of ECG monitoring before and after drug administration is warranted.[2] Before drug approval and registration by the EMA, clinical evaluation of QT/QTc prolongation and pro-arrhythmic potential for non-arrhythmic drugs is usually performed following the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) 14 guidelines. These thorough QT studies exclude patients with additional risk factors or a prolonged baseline QTc interval, so the QTc-prolonging effect of these drugs in critically ill patients with multiple risk factors is not studied. Additionally, according to these guidelines, ECG recordings are taken on specific time points around the T_{max}. However, the association between the occurrence of the maximum mean QTc increase from baseline and time after administration of the QTc-prolonging drug has not been extensively studied for many of the QTc-prolonging drugs. Drug effects are generally related to plasma concentrations with a maximum effect (E_{max}) on the T_{max} of the drug. The QTc interval may thus be maximally prolonged at the T_{max}, but there might also be a lag phase between peak plasma concentrations and maximum QTc prolongation.[3] Continuous analyses of high-frequency monitor data are needed to measure such drug effects and to provide a more solid basis for the timing of ECG monitoring.

QTc prolongation may not only be caused by QTc-prolonging drugs, but also by older age, female sex, heart diseases such as bradycardia, chronic heart failure, electrolyte disturbances such as hypokalaemia and hypomagnesemia, and renal dysfunction.[4–6] TdP mainly occurs when multiple risk factors inducing QTc prolongation are present. Risk factors for developing QTc prolongation and TdP in critically ill patients seem to be similar to those in the ambulatory population.[7–9] However, critically ill patients may be more vulnerable as several risk factors can be present at the same time. Therefore, it is important to know the prevalence of drug-induced QTc prolongation in the intensive care unit (ICU) population.[10]

Ciprofloxacin and erythromycin are both frequently used QTc-prolonging antibiotics in critically ill patients. Ciprofloxacin is a broad-spectrum second-generation fluoroquinolone and is mainly used intravenously (IV) in ICU patients to treat a number of bacterial infections. Ciprofloxacin was added to the QT drugs list in March 2015 resulting in many QT drug–drug interaction alerts. However, the QTc-prolonging effect of ciprofloxacin seems minimal when administered orally.[11–15] IV administration of ciprofloxacin, especially in critically ill patients, might increase the QTc-prolonging potential of ciprofloxacin. Erythromycin is a macrolide antibiotic and well-known for its QTc-prolonging effect.[16] However, in ICU patients, it is commonly administered in low dosages to treat delayed gastric emptying.[17] The QTc-prolonging effect of low-dose erythromycin is relatively unknown.[7,18,19]

To address these knowledge gaps, the primary objective of this study was to assess the time course of the QTc interval for at least 24 h during the use of IV ciprofloxacin and low-dose erythromycin in ICU patients. The secondary aim was to assess the characteristics of QTc interval dynamics, such as the association of the time to the longest QTc interval with the T_{max} of both drugs.

What is already known about this subject

- Fluoroquinolones and macrolides are both known to prolong the QTc interval and are listed on the CredibleMeds® QT drug list with a known risk of TdP by Arizona Centre for Education and Research on Therapeutics (AZCERT).
- It seems that ICU patients are prone to developing QTc interval prolongation.
- The association between the occurrence of the maximum mean QTc increase from baseline and time after administration of the QTc-prolonging drug has not been extensively studied for many of the QTc-prolonging drugs.

What this study adds

- Intravenous ciprofloxacin and low-dose erythromycin do not have a significant effect on the QTc interval over a 24-hour time interval in ICU patients.
- The QTc interval of ICU patients is highly variable over time.
- No recommendations as to the timing of ECGs after initiation for one or more QTc-prolonging drugs can be provided as our study lacks ECG recordings with substantial changes in the QTc interval over a dose interval, and a high variability of the QTc interval is found in this study.

2 | METHODS

2.1 | Study design and setting

The study was designed as an observational cohort study, in which a cohort of patients using ciprofloxacin or erythromycin IV (index group) was compared to a cohort of patients using no QTc-prolonging drugs (control group). Ciprofloxacin and erythromycin IV were only given as part of routine clinical care. The study was performed at the Intensive Care Units of Erasmus MC in Rotterdam, the Netherlands. The medical ethics review board of Erasmus MC approved the protocol (MEC-2016-407) and written informed consent was obtained from all individual participants/legal representatives prior to study initiation. The study was conducted according to the principles of the Declaration of Helsinki.

2.2 | Study population

Patients aged 18 years or older, using only ciprofloxacin or erythromycin IV as a potentially QTc-prolonging drug, were eligible for inclusion in the index group. Patients without the use of QTc-prolonging drugs, according to QT drugs list of drugs with a known risk of TdP of the Arizona Centre for Education and Research on Therapeutics,[1] were eligible for inclusion in the control group. If QTc-prolonging drugs with a known risk of TdP[1] were used before the study period, the QTc-prolonging drugs had to be fully eliminated before the patient was eligible for inclusion. A drug was considered to be fully eliminated after five times the elimination half-life (T½) of the drug.

Patients were excluded if one of the following conditions were present: congenital prolonged QTc syndrome, a (bi)ventricular implantable cardioverter defibrillator (ICD) or pacemaker, the presence of atrial fibrillation or other ECG abnormalities interfering with the QTc interval at baseline; for example, left and right bundle branch block. Patients were also excluded if they used QTc-prolonging drugs with a known risk of TdP. However, low-dose haloperidol IV of less than 5 mg per day was allowed in all groups, as haloperidol has no significant effect on QTc prolongation in low dosages.[20] Propofol was allowed in the erythromycin and erythromycin control group, as erythromycin was only prescribed in patients sedated with propofol.

2.3 | Outcome measures

The primary outcome measure of this study was the course of the QTc interval during a 24-hour dose interval of intravenous ciprofloxacin and erythromycin in ICU patients reported as 25^{th}–75^{th} percentiles. The secondary outcome measure was the effect of administration of ciprofloxacin and erythromycin IV determined by comparing an hour before the first administration (baseline) and an hour after the first, second, and third administrations. A QTc interval of 500 ms was used as a threshold to indicate clinically relevant QTc prolongation. Lastly, we studied the overall variability of the QTc intervals during 24 hours in both groups.

2.4 | Data collection

Ciprofloxacin and erythromycin IV were prescribed by physicians in the ICU according to standard institutional protocol. The dose regimen of ciprofloxacin IV was 400 mg three times daily with an infusion time of 30–60 min. The dose regimen of erythromycin IV was 100 mg twice daily with an infusion time of 30–60 min.

The following data were prospectively collected from the electronic patient data management system (version 8.3.2., PICIS, Wakefield, MA, used in the hospital until the June 21, 2017) or the patient's electronic medical record HiX (Chipsoft B.V., the Netherlands, used in the hospital from the June 23, 2017) depending on the inclusion period: general patient characteristics, liver and renal function parameters, serum electrolyte levels, acute physiology and chronic health evaluation (APACHE) scores, sequential organ failure assessment (SOFA) scores, concomitant medication, and dosages. Seventy-two hours of 200 Hz ECG telemetry data were collected from bedside monitors (Infinity M540, Drägerwerk AG & Co. KGaA) and converted to SynescopeTM (V3.10, ELA Medical; a sorin group company), a high-end ECG Holter analysis software including a QT-analysis module. The Dräger infinity system that was used is validated for the determination of QTc intervals. This module applied a 30-second averaging time for the waveform complexes. The QT interval was measured from the beginning of the QRS complex to the end of the T wave. The QRS intervals were averaged by synchronizing the start of the QRS complexes. Based on those mean waveforms, the software calculated the peak of the T wave using the parabola method. The end of the T wave was calculated by determining the intersection between the maximum decreasing tangent and the isoelectric line.[21,22] The analysis was performed automatically for all available leads. For the QT correction, the QT/RR linear regression analysis was conducted after precise manual beat classification and template correction with calculation of slopes and correlation coefficients (QT/RRcorr). Data points where no QTc value was registered due to low signal strength were excluded from the analysis. All values were manually checked for artifactual data.

Additionally, from the patient monitoring system heart rate data were registered at a rate of 1 Hz from 2 h before until 24 h after the start of ciprofloxacin and erythromycin therapy. Data averaging was 10 s for ECG-derived heart rate. A software tool was constructed in LabVIEW (version 2017 SP1, National Instruments) for time-based data stratification. All data were handled confidentially and stored in the electronic data capture (EDC) OpenClinica (OpenClinica©, LLC and collaborators, version 3.12.2).

2.5 | Statistical analysis

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS, IBM SPSS statistics V21.0) and R Software (R Foundation for Statistical Computing). For both groups standard statistical methods were used to calculate means and standard deviations (SDs) (for normally distributed variables), and medians and

interquartile ranges (IQRs) (for not normally distributed variables), as well as independent *t*-tests. The independent *t*-test was used to compare continuous variables, assuming equal or unequal variances between the two cohorts, and Chi-squared test or Fisher's exact test, as appropriate, was used for categorical variables.

Collected physiological data (per second) and the QTc values (per 30 s) were grouped in 60-minute timeframes. To provide an estimate of the effects of the therapy on the QTc values over time, several time intervals were included of which; an hour before the first administration (baseline) and an hour after the first, second, and third administrations. A QTc interval of 500 ms was used as a threshold to indicate clinically relevant QTc prolongation. The effect of administration of ciprofloxacin and erythromycin IV on the QTc interval was determined with a two-sample *t*-test for clustered data on all QTc values that were registered during the 26-hour study period. A linear mixed model by maximum likelihood was applied to adjust for the repeated measurements of QTc values. The fixed and random effects of the available time intervals and therapy on the QTc values were assessed. In accordance with pharmacokinetic studies, we estimated that 20 patients for the index group and 20 patients for the control group would be sufficient to study whether changes in the QTc interval prolongation follow the course of drug concentrations throughout a 26-hour time interval. Mean QTc intervals >500 ms were calculated per patient and tested between therapy and control groups using a Wilcoxon rank sum test.

2.6 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY,[23] and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18.[24]

3 | RESULTS

3.1 | Study population

In total, 71 patients were included for analysis; 14 patients were included in the ciprofloxacin group and 17 patients in the erythromycin group. In both control groups 20 patients were included. The flowchart with reasons for exclusion is shown in Figure 1. Patient characteristics of the different subgroups are shown in Table 1. The mean age of all patients was 54 years. Most patients in the erythromycin groups were male (85% and 77%, respectively). The APACHE II scores of the patients in the ciprofloxacin group were significantly higher than in the ciprofloxacin control group.

3.2 | Ciprofloxacin

Figure 2A,B shows the trends in heart rate and QTc interval during a 2-hour baseline period and throughout the 24-h period in which ciprofloxacin was administered in the index group, plotted together with the control group. A linear mixed model was fit with QTc values as the response variable, with fixed effects of therapy and the time intervals, and their relation to the individual patient. The model was fit by maximum likelihood, including random intercepts for the individual patient and random slopes for therapy and their interaction with the patient. The results are shown in Table 2. No evident effect over time on therapy was observed on the QTc interval.

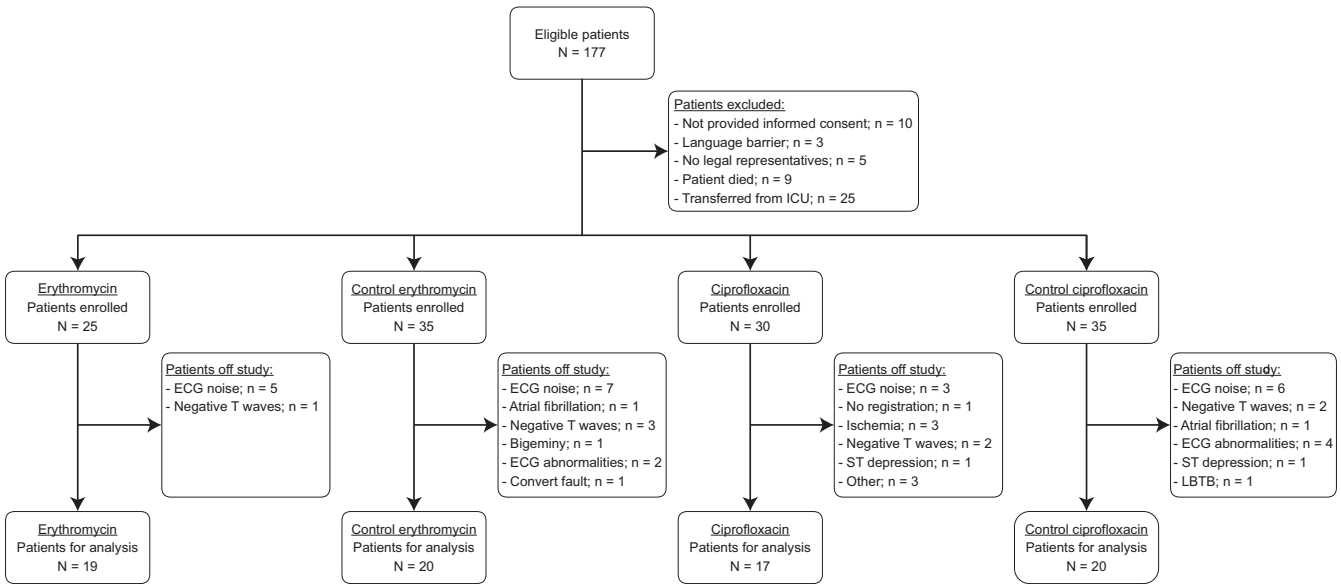

FIGURE 1 Flowchart of the results of inclusion and exclusion in the ciprofloxacin and erythromycin index and control groups

TABLE 1 Baseline demographics

Demographics	Ciprofloxacin n = 14	Control ciprofloxacin n = 20	*p* value	Erythromycin n = 17	Control erythromycin n = 20	*p*-value
Age (years), mean ± SD	54.6 ± 15.8	53.7 ± 13.7	.85†	50.1 ± 16.6	47.9 ± 20.0	.72†
≤50, n (%)	5 (35.7)	6 (30.0)	.73‡	8 (47.1)	10 (50.0)	.86‡
>50, n (%)	9 (64.3)	14 (70.0)		9 (52.9)	10 (50.0)	
Female sex, n (%)	7 (50.0)	8 (40.0)	.56‡	4 (23.5)	3 (15.0)	.68‡,*
BMI (kg/m^2), mean ± SD	26.7 ± 4.3	26.2 ± 4.8	.75†	24.7 ± 3.2	25.3 ± 2.4	.55†
Race, Caucasian, n (%)	10 (71.4)	17 (85.0)	.41‡	13 (76.5)	18 (90.0)	.38‡,*
Reason for admission, n (%)						
General medical	11 (78.6)	12 (60.0)	.26‡	8 (47.1)	9 (45.0)	.90‡
Surgical	2 (14.3)	5 (25.0)	.67‡,*	1 (5.9)	-	-
Emergency surgical	1 (7.1)	2 (10.0)	1.00‡,*	6 (35.3)	10 (50.0)	.37‡
SAH	—	1 (5.0)	—	2 (11.8)	1 (5.0)	.58‡*
Comorbidities, n (%)						
Hypertension	6 (42.9)	3 (15.0)	.07‡	4 (23.5)	3 (15.0)	.68‡*
Diabetes mellitus	2 (14.3)	2 (10.0)	.55‡,*	2 (11.8)	1 (5.0)	.58‡*
Myocardial infarction	—	1 (5.0)	—	—	1 (5.0)	—
Serum electrolyte parameters, n (%)						
Hypokalaemia (<3.5 mmol L^{-1})	—	1 (5.0)	—	1 (5.9)	—	—
Hyponatremia (<136 mmol L^{-1})	2 (14.3)	3 (15.0)	.67‡,*	3 (17.6)	—	—
Hypomagnesemia (<0.7 mmol L^{-1})	2 (14.3)	3 (15.0)	.62‡,*	1 (5.9)	2 (10.0)	.56‡,*
CRP, median (IQR)	103.8 (141.3)	93.0 (111.0)	.55†	88 (124)	43.9 (78.7)	.43†
Renal dysfunction, n (%)	3 (21.4)	—	—	4 (23.5)	2 (10.0)	.38‡,*
ICU length of stay until inclusion (in days), median (IQR)	1 (15.3)	2.5 (10.0)	.32†	3.0 (4.0)	0 (1.0)	.08†
APACHE II	23.1 ± 7.2	16.8 ± 5.8	.02†	20.4 ± 6.3	19.5 ± 6.0	.72†

Note: Missing values: APACHE II (ciprofloxacin n = 5, ciprofloxacin control n = 4, erythromycin n = 4, and erythromycin control n = 8); CRP (ciprofloxacin control n = 1); Mg (ciprofloxacin control n = 2); and eGFR (ciprofloxacin control n = 1).

Abbreviations: APACHE, acute physiology and chronic health evaluation; BMI, body mass index; CRP, C-reactive protein; ICU, intensive care unit; IQR, interquartile range; SAH, subarachnoid hemorrhage; SD, standard deviation.

†Independent t-test.

‡Chi-squared test.

*Fisher's exact test.

3.3 | Erythromycin

Figure 3A,B shows the heart rate and QTc interval during 26 h in the erythromycin index and control groups. As with ciprofloxacin there was no change in heart rate or increase in the QTc interval following the administration of erythromycin. A linear mixed mode was applied as described above, the results are reported in Table 2. Erythromycin had no clear effect on QTc interval over time.

3.4 | Variability

In this heterogeneous study population the QTc interval was highly variable within each of the groups, but did not vary between the groups, as shown in Figure 4. There was no significant difference ($p = 0.22$) in QTc values between the ciprofloxacin group (mean 393 ms) and ciprofloxacin control group (mean 386 ms). The erythromycin group (mean 405 ms) and erythromycin control group (mean 404 ms) neither showed a significant difference ($p = 0.80$). In 0.6%

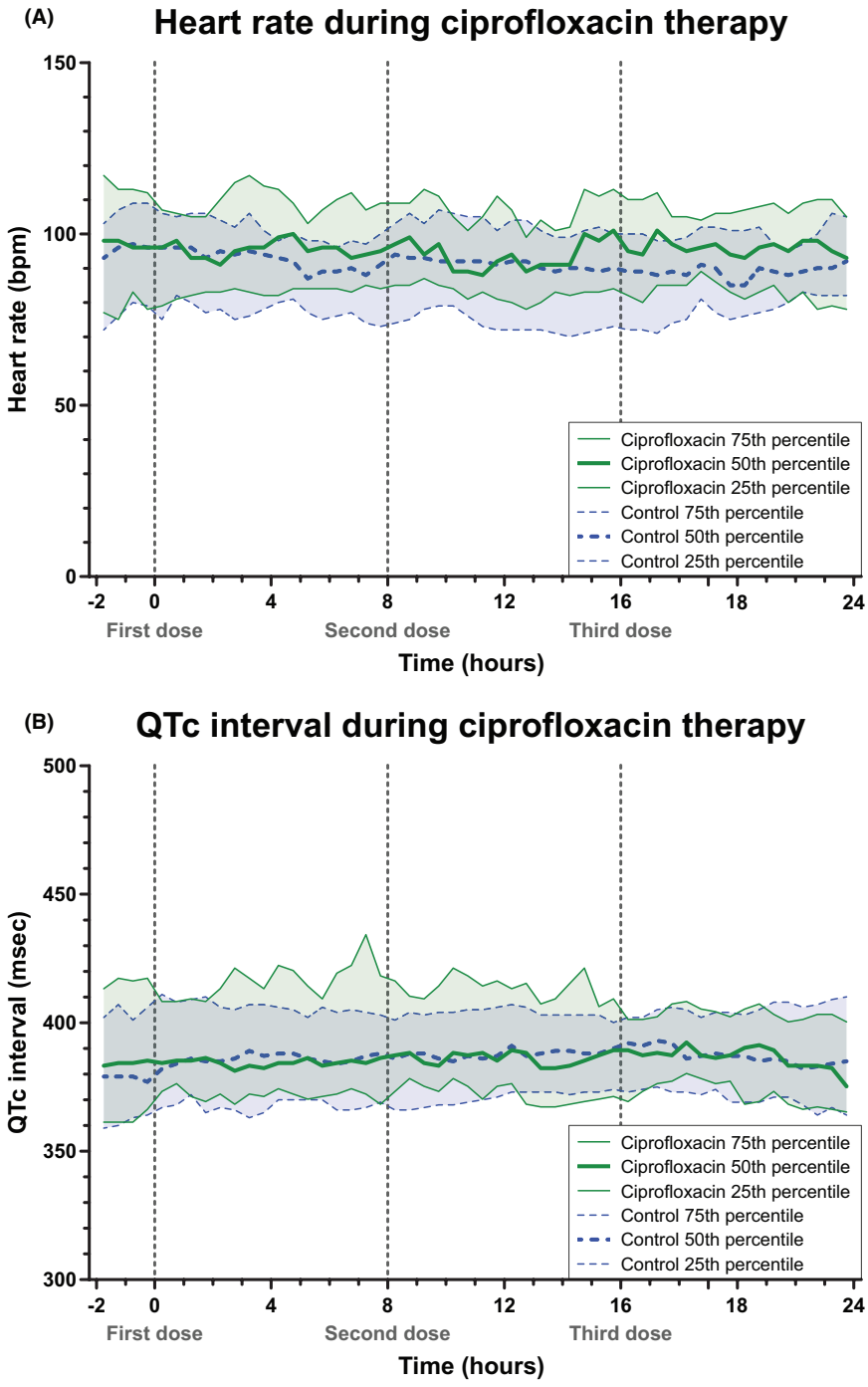

FIGURE 2 (A) Heart rate and (B) QT intervals of ciprofloxacin index (n = 14) and matched control (n = 20) group during a 2-h baseline period, followed by 24 h of ciprofloxacin therapy with three intravenous administrations of ciprofloxacin as indicated by the vertical dotted lines. Trend lines indicate the 25th, 50th, and 75th percentiles

of the registrations (1.138 out of 198.270 samples) the duration of the QTc interval was longer than 500 ms. The index groups showed slightly more recorded QTc intervals over 500 ms (ciprofloxacin 1.2% and erythromycin 0.8%) than the control groups (ciprofloxacin control 0.2% and erythromycin control 0.3%). However, QTc intervals >500 ms were not significantly different between therapy and control groups: ciprofloxacin therapy group (n = 7), median 531 (IQR 518–540) ms versus control group (n = 14), median 524 (IQR 515–531) ms; $p = 0.36$ and erythromycin therapy group (n = 13), median 525 (IQR 516–545) ms versus control group (n = 16), median 521 (IQR 516–544) ms; $p = 0.71$.

4 | DISCUSSION

This study showed no changes in the duration of the QTc interval in patients in whom ciprofloxacin or erythromycin was administered intravenously. Despite the fact that ECG was continuously recorded and the administration of both antibiotics carefully timed, no changes were observed. The index groups showed slightly more recorded QTc intervals over 500 ms (ciprofloxacin 1.2% and erythromycin 0.8%) than the control groups (ciprofloxacin control 0.2% and erythromycin control 0.3%).

For ciprofloxacin it was expected that some changes would be observed, as this antibiotic has been mentioned to be associated with

TABLE 2 Estimated fixed effects of the maximum likelihood linear mixed model

	Fixed effect	Estimate	95% CI	Std. Error	*t*
Ciprofloxacin	Intercept	387.64	377.86–397.43	4.85	79.92
	Time interval	0.10	0.06–0.14	0.02	4.56
	Therapy	2.05	−4.38–8.52	3.07	0.67
Erythromycin	Intercept	398.82	389.36–408.28	4.70	84.83
	Time interval	0.40	0.36–0.44	0.02	19.07
	Therapy	2.27	−5.86–10.39	3.91	0.58
	Random effect	**Type of effect**	**Variance**		**Std. Dev.**
Ciprofloxacin					
	Individuals	Random intercept	797.2		28.2
	Therapy	Random slope	125.6		11.2
	Residuals		254.1		15.9
Erythromycin					
	Individuals	Random intercept	815.7		28.6
	Therapy	Random slope	256.4		16.0
	Residuals		277.4		16.7

Abbreviations: CI, confidence interval; Std. Dev., standard deviation; Std. Error, standard error.

QTc prolongation.[25] In line with our data, also Heemskerk et al could not find a QTc-prolonging effect of ciprofloxacin and they concluded that it is unlikely that ciprofloxacin has a clinically relevant QT prolonging effect or an increased risk of TdP.[15] Also in a recent drug–drug interaction study performed by our group, we found that the prevalence of QTc prolongation in patients using a combination of ciprofloxacin with fluconazole was low.[26] As a consequence, ciprofloxacin can be removed from lists used for medication surveillance. ECG monitoring does not seem to be necessary for ciprofloxacin.

Erythromycin is a macrolide antibiotic, often used as a prokinetic in ICU patients. Like the other macrolides, erythromycin has been associated with severe QTc interval prolongation. Especially when erythromycin is co-administered with other drugs that inhibit or are substrates of the CYP3A4 enzyme, the patient is at risk for severe QTc prolongation and subsequent risk of QT-related malignant arrhythmia.[27] Twenty-five years ago, Oberg et al, reported an impressive increase from baseline QTc of 432 ± 39 ms to 483 ± 62 ms during erythromycin therapy.[28] Overall, 19 (39%) of 49 patients in their study had a moderate to severe delay in ventricular repolarization (QTc ≥ 500 ms). The dosages of erythromycin were much higher than those in our study, and ranged from 18 to 83 mg kg^{-1} day^{-1}. In our study, the erythromycin dosages ranged from 2 to 4 mg kg^{-1} day^{-1}.

Fiets et al also studied 51 ICU patients treated with erythromycin as a prokinetic (dose: 200 mg bid IV).[19] In this study continuous ECG recording was not used, but standard 12-lead ECGs were recorded directly before, and 15 min after the first infusion of erythromycin, as well as 15 min after the third infusion. The QTc interval increased significantly from 430 ms at baseline to 439 ms ($p = 0.03$) after 15 min and 444 ms ($p = 0.01$) after 24 hours. No QTc-related arrhythmias were observed. Possibly the difference in outcome with our study, where we did not find changes in the QTc interval, is caused by the fact that the erythromycin dose used by Fiets et al (200 mg b.i.d.) was twice as high as the dose in our study (100 mg b.i.d.).

Our population included patients with traumatic brain injury and (aneurysmatic) subarachnoid hemorrhage (SAH). SAH often causes a prolongation of the QTc interval during the acute phase.[29,30] However, we analyzed the SAH patients separately and did not find a significant difference in QTc prolongation between SAH patients and other patients.

A diurnal pattern in heart rate and QTc interval has been reported, related to autonomic regulation of ventricular repolarization, but a circadian rhythm was not observed in our patient population. Most likely this is due to the fact that we studied an intensive care population in whom the day/night activity cycle can be disturbed. Also, the heart rate was constant for all patients during the 26-hour time interval.

One of the hypothesis at the start of the study was that after a drug dose the degree of QTc interval prolongation would be related to the plasma concentration, either directly or with some delay. This might be important for timing of ECGs to check if, and to what degree, QTc interval prolongation has occurred following one or more doses of the drug. Our study cannot provide recommendations as to the timing of ECGs after initiation for one or more QTc-prolonging drugs, as our study lacks ECG recordings with substantial changes in the QTc interval over a dose interval and a high variability of the QTc interval is found in this study.

An important strength of our study is the continuous recording of ECGs in patients admitted to the ICU. There are numerous QT correction formulae to compare measurements at different time points and at different heart rates. Vandenberk et al. suggested that the correction formulae of Fridericia and Framingham have the best

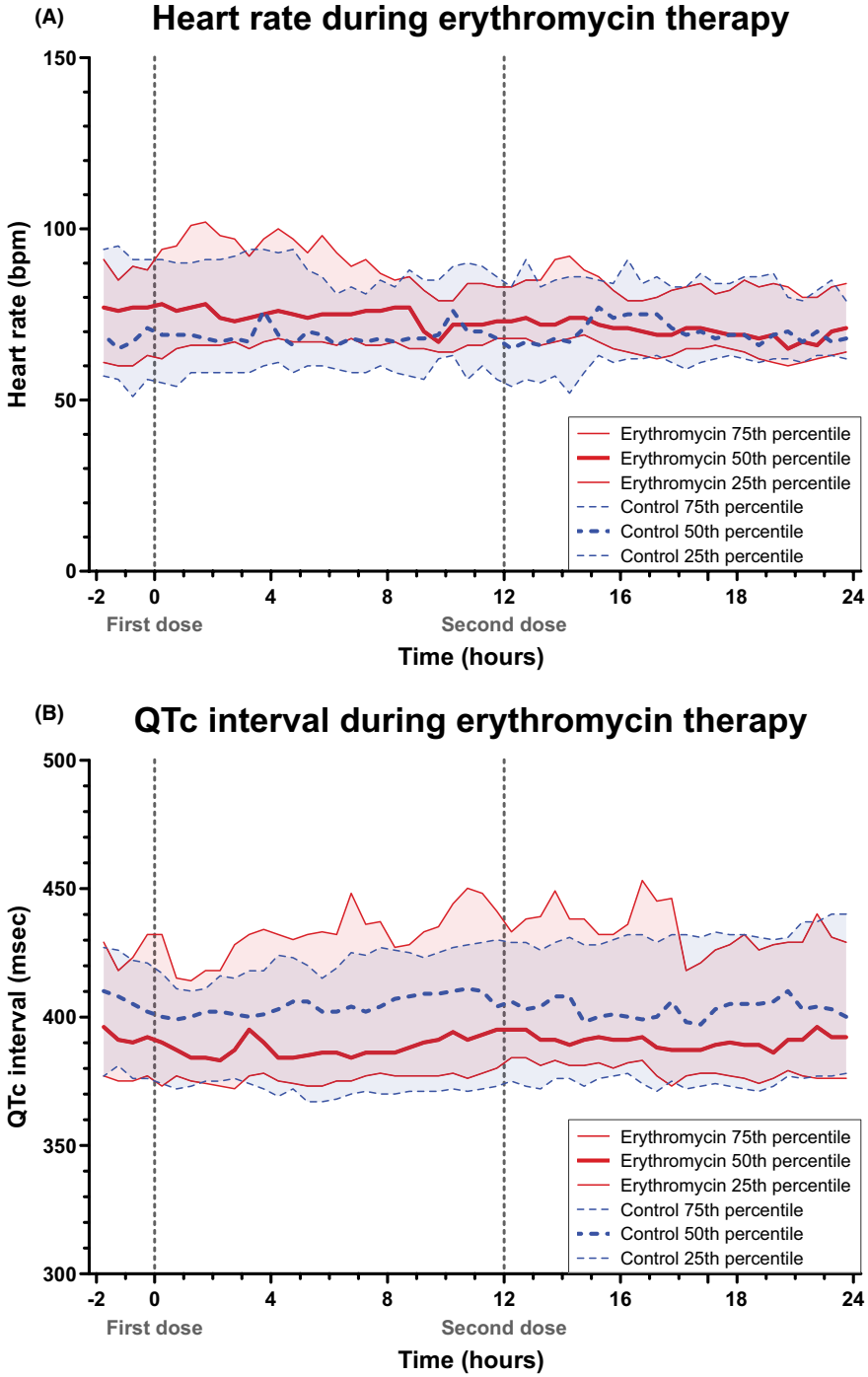

FIGURE 3 (A) Heart rate and (B) QT intervals of erythromycin index (n = 17) and matched control (n = 20) group during a 2-h baseline period, followed by 24 h of erythromycin therapy with three intravenous administrations of ciprofloxacin as indicated by the vertical dotted lines. Trend lines indicate the 25th, 50th, and 75th percentiles

rate correction and are significantly associated with 30 day and 1-year mortality. However, Robyns et al. showed that individualized corrected QTc intervals derived from continuous ECG recordings are superior to conventional QTc intervals measured from a standard 12-lead ECG when using linear regression with QT-RR plots used in this study.[31]

Furthermore, the timing of administration of the intravenously administered ciprofloxacin and erythromycin was carefully recorded. Although this type of monitoring would have allowed the detection of even subtle or temporary changes in the QTc interval, such changes were not found in our study. This brings us to the most important weakness of the study, that is, the lack of a positive control. At the start of the study it was our hypothesis that we would find a positive signal of QTc prolongation following the IV administration of these drugs. Ideally we would have wanted to see QTc interval changes, albeit temporarily, following administration of a well-known QTc-prolonging drug. Although it was expected that the erythromycin-treated patients would show at least some degree of QTc prolongation after infusion of this drug we did not find any effect. Due to the absence of a control group, it cannot be ruled out that the lack of QTc prolongation in both treatments is related to an inadequate sensitivity of the study to detect variations of 10 ms.

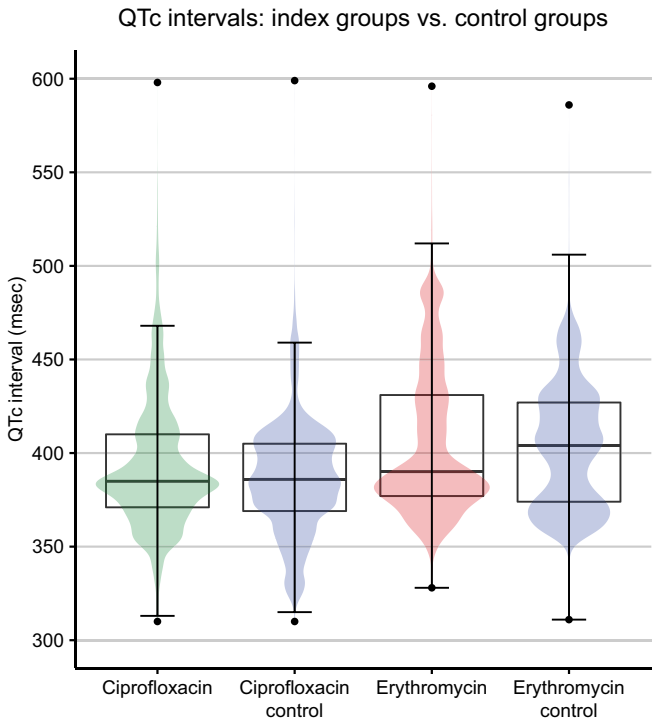

FIGURE 4 Violin plot of QTc intervals (in milliseconds) in the ciprofloxacin (n = 36.989 samples) and erythromycin (n = 47.754 samples) index groups and their respective control groups (n = 55.511 and n = 58.016 samples). Boxes indicate the median and interquartile range, whiskers indicate the standard error. Dots indicate the minimum and maximum values of the range. No significant differences were found between the index and control groups

However, the equipment used in this study is certified and validated for QTc prolongation detection. The statistical analyses are corrected for multiple measurements per patient, variance within groups and between therapy groups. The sensitivity of this study for detecting QTc alterations between therapy groups is technically and statistically sufficient, so a detection capacity problem seems unlikely. Another noteworthy finding of this study is that the pattern of intra-treatment variability of the QTc interval shows higher variability and high dispersion in the control population. This could be caused by inadequate control groups, but as shown in Figure 1, no differences were found between the index and the control groups, except for the higher APACHE II score in the ciprofloxacin index group, which is not an explanation for the differences in variability. It should also be noted that we limited our QTc interval assessment to the first 24 h of drug administration and drug accumulation can be expected with continuation of the treatment. Therefore, our data cannot be extrapolated to circumstances in which accumulation occurs. However, we expected at least some degree of QTc prolongation after infusion of both drugs in the first 24 h and it seemed unlikely that significant QTc prolongation would only occur after 24 h.

To conclude, intravenous ciprofloxacin and low-dose erythromycin do not have a significant effect on the QTc interval over a 24-h time interval in ICU patients. Hence, we advise no routine ECG monitoring when ciprofloxacin 400 mg t.i.d. and low-dose erythromycin 100 mg b.i.d. are used in ICU patients who have no electrolyte abnormalities and no other QTc-prolonging drugs.

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CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

PvdB, TvG, and FB have made substantial contributions to conception and design. FB and WvW were responsible for acquisition of data and data analysis. Data interpretation was performed by FB, NdG, WvW, and TvG. HvdS, JB, NH, and NdG have been involved in revising the manuscript critically for important intellectual content. All authors have given final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Florine A. Berger https://orcid.org/0000-0003-2723-8919
Willem van Weteringen https://orcid.org/0000-0003-2667-3169
Heleen van der Sijs https://orcid.org/0000-0002-1744-0999
Nicole G. M. Hunfeld https://orcid.org/0000-0001-6856-7028
Jeroen J. H. Bunge https://orcid.org/0000-0002-7897-4628
Natasja M. S. de Groot https://orcid.org/0000-0002-0259-6691
Patricia M. L. A. van den Bemt https://orcid.org/0000-0003-1418-5520
Teun van Gelder https://orcid.org/0000-0001-5980-6947

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