QTc prolongation during erythromycin used as prokinetic agent in ICU patients

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ABSTRACT

Background High-dose erythromycin used as antibiotic prolongs QTc interval. Low-dose erythromycin is frequently used as a prokinetic agent, especially in patients in the intensive care unit (ICU). It is unknown whether low-dose erythromycin affects cardiac repolarisation and puts patients at risk for torsades de pointes.

Methods In this prospective study, we included ICU patients treated with erythromycin as prokinetic in a dose of 200 mg twice a day. An ECG was performed before, 15 min and 24 hours after the start of erythromycin. Cardiac repolarisation was assessed by rate-corrected analysis of the QT interval (QTc) on the ECG by two independent investigators. Starting or stopping other possibly QTc prolonging drugs during the study period was an exclusion criterion. Wilcoxon signed-rank test and Friedman's test were used for statistical analysis to assess prolongation of QTc. Primary outcome was defined by the prolongation of QTc after 15 min and 24 hours.

Results 51 patients were eligible for this study. In these patients, QTc 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. After 15 min and 24 hours, the upper limit of 95% CI for prolongation of QTc was well above 10 ms. No QTc-related arrhythmias were seen.

Conclusions During treatment with erythromycin in a dose of 200 mg twice a day, QTc prolonged mildly but significantly. Sequential ECG registration should be performed when low-dose erythromycin is prescribed, especially in the presence of other risk factor for QTc prolongation.

INTRODUCTION

Low-dose erythromycin is commonly used as a prokinetic agent in critically ill patients. The usual recommended dose is 200 mg twice a day. Erythromycin is found to be more effective than metoclopramide in decreasing gastric residue.¹ In the comparatively higher antimicrobial dose (ie, four times a day 1000 mg), erythromycin is known to prolong the QT interval, the heart rate-corrected QT interval (QTc) and increases the risk of torsades de pointes (TdP) and sudden cardiac death.² In this context, a QTc prolongation of up to 50 ms has been noted and the incidence of sudden cardiac death was found to be twice as high in patients receiving erythromycin as compared with amoxicillin.^{3–5} Combined with CYP3A4 inhibitors, like azole antifungal drugs, diltiazem and verapamil, the incidence was even five times increased.⁵ QTc

prolongation due to erythromycin is caused by its ability to block the human ether-a-go-go-related potassium channel, which plays a pivotal role in cardiac repolarisation and QTc prolongation.⁶

It is unknown whether erythromycin in a prokinetic dose prolongs QTc. One study showed that erythromycin is associated with prolonged QTc in intensive care unit (ICU) patients, but the mean dose in this study was 321 mg, slightly higher than the usual prokinetic dose.⁷ On the contrary, another study using erythromycin 400 mg twice a day for cystic fibrosis bronchiectasis failed to show an increase in QTc.⁸

Therefore, we assessed the effect of low-dose erythromycin used as a prokinetic on QTc and the occurrence of TdP.

METHODS

Study design

In this prospective observational single centre study, between April 2013 and June 2014, we included patients who were admitted to the ICU and administered erythromycin in a prokinetic dose, that is, twice a day 200 mg intravenously. An ICU population was chosen because of the frequent use of erythromycin as prokinetic agent.

Setting

Erythromycin 200 mg was dissolved in 100 mL NaCl 0.9% and given in 30 min intravenously and prescribed in combination with metoclopramide to enhance its prokinetic effect.

Standard 12-lead ECGs were registered by ICU nurses directly before, 15 min after the first infusion of erythromycin and 15 min after the third infusion (which is after 24 hours). The last is considered as the steady state.

The study was approved by the local ethics committee. The institutional review board waived the need for informed consent due to the observational character of the study.

Study population

All patients who received erythromycin used at a prokinetic dose, that is, 200 mg twice a day, between April 2013 and June 2014 were included. Exclusion criteria were as follows: (1) erythromycin in doses other than 200 mg twice a day and (2) initiation of other QTc prolonging medication on day 0 according to Arizona list 1, as well as (3) the discontinuation of QTc prolonging medication on day 0.

Outcomes

Primary outcome was defined as the prolongation of QTc after 15 min and 24 hours. Secondary

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outcomes were defined as the absolute prolongation of QTc and the absence of TdP. An increase in mean QTc prolongation with an upper boundary of the 95% CI of more than 10 ms was considered to be clinically significant according to the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline.⁹ Furthermore, risk factor for potential QTc prolongation was assessed.

Data collection

ECG hardcopies were analysed by two clinicians (RBF and EJPL) by measuring QT intervals manually followed by calculation of QTc according to Bazett's formula, that is, $QTc = QT/RR^{1/2}$ and a mean QTc was derived from both measurements and used for further analysis to correct for individual deviation.

In all patients, plasma levels of creatinine, potassium (normal range 3.5–4.8 mmol/L) and magnesium (normal range 0.7–1.1 mmol/L) were obtained and aspects of hepatic dysfunction (defined as a clinical diagnosis by the intensivist or an alanine transaminase (ALAT) $\geq 2.5 \times$ upper limit of normal (ULN=45 U/L) and bilirubin ≥ 1.5 ULN (ULN=17 μ mol/L)) and the need for haemodialysis were recorded. Apache II score was calculated on admission. Medication was screened for most potent CYP3A4 inhibitors (amiodarone and voriconazole) and other QTc prolonging drugs, using Arizona list 1 (drugs with known TdP risk) as reference.¹⁰ Renal dysfunction was defined as a creatinine clearance of <30 mL/min/1.73 m² estimated by Modification of Diet in Renal Disease 4 or being treated with renal replacement therapy.

During therapy, all patients were continuously monitored for cardiac arrhythmias (TdP, but also atrial fibrillation and ventricular tachycardia).

Statistics

We used IBM SPSS V.20 for statistical analysis. Bland-Altman plot was used to measure interobserver agreement and for the three ECGs with highest difference between observers compromise was achieved after critical re-evaluation. Intraclass correlation coefficient was used to define correlation between QTc between different observers, that is, Cronbach's α .

Because our data were better represented by the median, we chose to use non-parametric tests.

The Wilcoxon signed-rank test was used to measure differences between mean QTc (of both observers) before and after erythromycin. Friedman's test was used to determine whether patients' QTc was significantly prolonged after 15 min and 24 hours. The Mann-Whitney U test was used for comparison of difference in QTc between different groups, between sex, hepatic or renal dysfunction, use of other QTc prolonging medication or CYP3A4 inhibitors.

RESULTS

A total of 70 patients were screened for eligibility (figure 1). In 60 patients, all three ECGs were recorded. In eight patients, the third ECG was missing or erythromycin was stopped before this ECG could be recorded. For two patients, the second ECG was missing. Eight patients received new QTc prolonging medication between day 0 and day 1. In three patients, QTc prolonging medication was stopped.

In a total of 51 patients, three ECGs were recorded and no change in QTc prolonging medication was made. Twenty-eight patients did not receive any QTc prolonging medication other than low-dose erythromycin during the study. Twenty-three patients remained on the same dose of QTc prolonging medication.

Patient characteristics are shown in table 1.

Figure 1 Flow chart.

Table 1 Patient characteristics of the included 51 patients

Patients (n=51)	
Age, year	
Mean	66.5
Range	32–85
Male sex, n (%)	33 (65)
Surgical patients, n (%)	25 (49)
CVVH, n (%)	16 (31)
MDRD* <30 , n (%)	4 (8)
Atrial fibrillation, n (%)	8 (16)
Hepatic dysfunction, n (%)	9 (18)
CYP3A4 inhibitors, n (%)	12 (24)
Other QTc prolonging medication, n (%)	23 (45)

*Modification of Diet in Renal Disease (MDRD), excluding patients on Continuous veno-venous hemofiltration (CVVH).

Mean difference in QTc between both observers was 14 ms (range: -102 ms to $+134$ ms, SD 47.9 ms). Cronbach's α measured for consistency between observers for all ECGs combined was 0.684, indicating acceptable internal consistency. The three ECGs with most difference between observers were discussed and consensus was made. QTc measured by both investigators was averaged and this QTc was used for further examination.

Change in QTc of all 51 patients is seen in figure 2.

QTc before medication was 430 ms (± 43 ms), 439 ms (± 43 ms) after 15 min and 444 ms (± 42 ms) after 24 hours. Median QTc at baseline was 422 ms, 438 ms after 15 min and 441 ms after 24 hours.

After 15 min and 24 hours QTc significantly increased using Friedman's test ($p=0.04$).

Figure 2 Absolute change in QTc after 15 min and 24 hours. X axis shows individual patients and Y axis shows increase or decrease in QTc after 15 min (blue) or 24 hours (red).

QTc significantly increased after 15 min with 9 ms (± 35 ms) ($p=0.03$) with a 95% CI between 0.8 and 16.2 ms. After 24 hours, QTc increased with 14 ms (± 44) ($p=0.01$) with a 95% CI between 4.0 and 24 ms compared with QTc before erythromycin.

Compared with baseline, QTc increased in 28 patients after 15 min and in 35 patients after 24 hours. No significant difference in baseline QTc was seen between both groups.

In four patients, QTc increased above 500 ms after 15 min or 24 hours. In three patients, QTc was already above 500 ms at baseline, so in a total of seven patients QTc was above 500 ms.

In the four patients with an increase in QTc above 500 ms, baseline QTc was 492 ms, 470 ms, 375 ms and 480 ms, respectively. When all three patients with QTc already above 500 ms were excluded, increase in QTc was still significant.

In the seven patients with a QTc above 500 ms, five patients were male, one had hepatic dysfunction, three had renal dysfunction, five used QTc prolonging medication (all amiodarone) and five used CYP3A4 inhibitors (all amiodarone). Four patients had a history of cardiac disease and one patient had hypomagnesaemia (magnesium of 0.62 mmol/L). Three of these patients had an increase in QTc with more than 50 ms.

Eight patients had an increase of QTc >50 ms after 15 min or 24 hours. In these eight patients, four patients were male, three had hepatic dysfunction, four had renal dysfunction, five used QTc prolonging medication and CYP3A4 inhibitors (all amiodarone). Four patients had a history of cardiac disease and one patient had a hypomagnesaemia (0.62 mmol/L). Three of these patients had an increase to >500 ms.

In the three patients with both an increase in QTc to >500 ms and with an increase of >50 ms, two patients were on amiodarone and the other one had hypomagnesaemia.

The Mann-Whitney U test did not reveal any statistical difference in the prolongation of QTc between sex of patients, patients with renal or hepatic dysfunction or on other QTc prolonging medication or CYP3A4 inhibitors (voriconazole and amiodarone). Only four patients had electrolyte disturbances: three had hypokalaemia and one had hypomagnesaemia. This number was too low to perform statistical analysis. When the patients using amiodarone ($n=11$) were excluded, the prolongation of QTc was not significant.

No new dysrhythmia after administration of erythromycin was seen.

In only 42 patients, Apache II score was available. The mean Apache II in these patients was 22.2 ranging from 3 to 44.

DISCUSSION

In this study, we showed that erythromycin in a low dose (200 mg twice a day intravenously) used as prokinetic agent

significantly increases QTc in ICU patients. In our study, during erythromycin QTc prolonged with a mean of 9 ms after 15 min and 14 ms after 24 hours, with an upper bound of the 95% CI well above 10 ms. Furthermore, seven patients (14%) developed a QTc of more than 500 ms, considered to be at the highest risk for developing TdP. The ICH Harmonised Tripartite Guideline states that an increase in mean QTc prolongation with an upper boundary of the 95% CI of more than 10 ms is considered to be clinically significant.⁹

Other studies in ICU populations found prolongation of QTc above 500 ms in 13%–40% of patients, partially caused by medication.^{7 11 12} Prolongation of QTc in ICU is associated with longer lengths of hospitalisation and increased mortality.¹³ Still, the combination of erythromycin and metoclopramide is proven to be most effective in decreasing gastric residue in ICU patients. Current guidelines advise this combination as prokinetic therapy in ICU patients^{14 15}

Study limitations

The observational before–after design provides a potential drawback for our study results. Ideally, we should have included a positive control, but we found giving for instance moxifloxacin for this reason not ethically justified in this vulnerable study population. A placebo controlled trial was not feasible due to lack of alternatives for erythromycin as prokinetic therapy and early timing of enteral feeding is equally associated with better outcomes.¹⁶ Some of the patients used CYP3A4 inhibitors (such as voriconazole or amiodarone), which might have increased the blood concentration of erythromycin and contributed to the QTc prolongation. However, the effect on QTc was already seen after 15 min, and at this time point the effect of CYP3a4 inhibition is nearly absent. Increase in QTc was not significantly more in patients on amiodarone or voriconazole. When patients on amiodarone ($n=11$) were excluded, the increase in QTc was not significant anymore. However, due to the small size of our study, these subgroup analyses have insufficient power to draw firm conclusions. It is known that the incidence of TdP in patients on amiodarone is remarkably low despite its ability to prolong QTc.¹⁷ This means that the risk assessment due to the small increase of erythromycin should be based on individual patient characteristics. In addition, there are other factors influencing QTc at the ICU, such as hypothermia, myocardial ischaemia or brain surgery, which we did not assess in our study.¹⁸ There is a possibility that these factors might influence the magnitude of QTc elongation of erythromycin. To dissect the influence of these variables, a larger study should be performed. Our study was too small to address these issues. We wished to study the influence of erythromycin used on the ICU in normal clinical practice and for this reason did not exclude all these possible influencing factors.

Erythromycin is commonly used in ICU patients so we considered this study group to be the most representative. Mean Apache II score of 22.3 showed a representative ICU population. To our information, there is no clear relation between QTc and Apache II scores.

In every study patient, erythromycin was combined with metoclopramide, which is common practice for this indication in ICU patient. Metoclopramide is only in very few case reports associated with prolonged QTc,¹⁹ but we cannot rule out metoclopramide-effected QTc in our patients.

Usual risk factors for QTc prolongation are gender, age, electrolyte abnormalities and other QTc prolonging medication.^{12 20} In our study, univariate analysis could not find any of these risk factors for QTc prolongation with erythromycin, probably due

to small group size. Factors associated with altered pharmacodynamics of erythromycin like renal or hepatic dysfunction were also not found to be of influence. Two patients used strong CYP3A4 inhibitors (namely azole antifungal medication). Furthermore, we showed that 15 min after administration, QTc was already significantly prolonged, which will be unrelated to CYP3A4 inhibition.

QTc assessment

We chose to assess the cardiac depolarisation by manually measuring QTc. Automated QTc measurement is usually not recommended because it can underestimate QTc.²¹ Only recently continuous QTc measurement was validated in critically ill patients, but only in patients with QRS <120 ms.²² Measurement of QTc is a complicated procedure which include pitfalls like assessment of the end of the T wave, U waves and bundle branch block.^{23–25} Studies showed that most physicians cannot properly recognise a prolonged QTc.²⁶ However, with a simple training inexperienced ECG readers were able to recognise prolonged QTc better than cardiologists and non-cardiologists.²⁷ Although the investigators were not QTc experts, they were sufficiently trained on measuring QTc. We choose to use the Bazett formula because it is the most frequently used in clinical practice and medical literature and is advised in the ICH guidelines, although some studies showed that Hodges and the Karjalainen-Nomogram are less heart rate dependent, compared with the Fridericia method and Bazett formula.^{28–29}

Dose dependency

In antimicrobial high-dose erythromycin, QTc prolongation varies between 30 and 50 ms.^{3–4} In our study, the 200 mg twice a day dose increases QTc between 9 and 14 ms. Erythromycin in a even lower dose of 70 mg twice a day has been found to be an equally effective prokinetic as in a dose of 200 mg twice day.³⁰ This study did not assess QTc. Since this study showed that there seems to be no clear dose–effect relationship in prokinetic effect, our findings advocate the use of this lower dose erythromycin, thus possibly avoiding the risk of QTc prolongation.

CONCLUSION

In our study, we found that during treatment with erythromycin in a prokinetic dose QTc significantly prolongs in ICU patient. Since this increase exceeds the upper limit of 95% CI with more than 10 ms and increases QTc to above 500 ms, this increase is clinically significant. Low-dose erythromycin should be used

with regular sequential assessment of QTc times on ECG in all ICU patients, especially in patients with other QTc prolonging risk factors. Since erythromycin 70 mg twice a day is found to be equally effective, this dose may be preferable for these patients. Future research should be performed to assess what is the effect of this lower dose on QTc time.

Contributors All authors, as listed, contributed significantly to this manuscript.

Competing interests None declared.

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What this paper adds

What is already known on this subject

High-dose erythromycin is known to prolong QTc and puts patients at risk for torsades des pointes. For low-dose erythromycin, although commonly used as prokinetic therapy in intensive care units (ICUs), this risk is unknown.

What this study adds

Our study showed that erythromycin used in a prokinetic dose prolongs QTc in ICU patient. ECG should be assessed for QTc prolongation in patients on erythromycin, especially in the presence of other risk factors for QTc prolongation.

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