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ORIGINAL REPORT

Erythromycin Prolongs the QT_c Interval Among Patients with Pneumonia

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SUMMARY

Erythromycin is commonly used to treat simple community-acquired pneumonia. We measured the prolongation in QT_c intervals in EKGs associated with intravenous erythromycin administration among patients hospitalized for simple pneumonia (DRGs 89 and 90). We reviewed the medical records of 50 patients who received at least 5 days of intravenous erythromycin, and found 15 with readable paired EKGs, at least one taken during the period of erythromycin administration and at least one other obtained when the patient had no erythromycin. The mean QT_c interval in lead II for EKGs taken without erythromycin was 0.422 s and the average prolongation of the QT_c interval associated with erythromycin administration was 0.046 s ($P < 0.01$). The administration of erythromycin was thus associated with an increase in QT_c intervals to a mean of 0.468 s, a value considered to be abnormally prolonged. We conclude that erythromycin prolongs the QT_c interval among patients hospitalized with pneumonia in the same manner previously reported for healthy volunteers in an experimental setting. The magnitude of this erythromycin-induced QT_c prolongation raises QT_c intervals into the abnormal range. Although no patient in this small study suffered an adverse effect from the QT_c prolongation, the magnitude of this effect is sufficiently large to raise clinical concerns. © 1997 by John Wiley & Sons, Ltd.

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INTRODUCTION

There are multiple case reports of prolongation of the QT_c interval and ventricular tachycardia in association with intravenous administration of erythromycin.[1–6] These idiosyncratic adverse effects of erythromycin on the QT_c interval are rare and not currently predicable. There is also a reproducible physiologic effect of erythromycin on the QT_c interval in *in vitro* cardiac preparations and in normal volunteers, although the clinical relevance of this observation is unknown. Experimental evidence suggests that the mechanism for the erythromycin-induced prolongation of the QT_c interval is similar to that reported for quinidine.[6–10] Although erythromycin is frequently used to treat pneumonia, to date there is no information concerning potential general adverse cardiac effects of erythromycin in a general clinical setting. In order to determine if there was a measurable effect of intravenous erythromycin on the QT_c interval in a clinical setting we undertook a systematic review of changes in QT_c intervals on standard 12-lead EKGs among patients in our hospital who received intravenous erythromycin for simple pneumonia. For each study subject we compared the QT_c intervals on standard 12-lead

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EKGs taken during a period of erythromycin administration with the QT_c intervals on similar EKGs obtained at other times with no erythromycin exposure.

METHODS

Identification of potential study patients

Many factors including electrolytes and medications are known to affect the QT_c interval. In addition, many of the diagnoses represented by the thousands of codes in the International Classification of Diseases (ICD-9) may also affect the QT_c interval, but this has not been systematically investigated. Unlike normal volunteers, hospitalized patients all have diagnoses of disease and receive medications. In order to minimize potential confounding by different diseases, especially cardiac disease, and medications used to treat them, we restricted our study population to patients with simple pneumonia as the reason for admission. We used an automated record linkage system containing pharmacy order data, ICD-9 coded discharge diagnoses, and Diagnosis Related Groups (DRGs) for admissions from 1988–1993 from Brigham and Women's Hospital to select patients for this study.[11] We identified patients in DRGs 89 and 90 (Simple Pneumonia) who also had pharmacy orders for intravenous erythromycin on at least 2 days during that admission. We further specified that the study patients must not have been dispensed either quinidine or procainamide during that admission. A total of 312 potential study subjects were identified in this manner.

Selection of medical records for review

We planned to limit potential confounding by restriction through selection of patients with a *primary* diagnosis of simple pneumonia (not other disease) and further excluded those who were given common antiarrythmics known to affect the QT_c interval. The resulting group consisted of patients with a primary diagnosis of pneumonia, and excluded those with a primary diagnosis of any other disease, common treatment for heart disease, or a secondary diagnosis of pneumonia. By selecting for simple pneumonia and against heart disease we substantially lowered the probability that any particular study subject would have multiple EKGs included in the medical record. To identify the medical records that would be most likely to contain an EKG obtained during the period of erythromycin administration, we selected those patients among the 312 potential study subjects whose electronic pharmacy records indicated that they had orders for the most days of intravenous erythromycin, beginning with the patients who had electronic pharmacy records for the longest courses. One of the first 50 records we requested could not be located, so ultimately we had to request 51 records to obtain the 50 subjects with simple pneumonia included in this study. Of the 50, 43 study subjects had electronic orders for at least 10 days of intravenous erythromycin, and all had electronic records of orders for at least 5 days. The dosage received by each patient was taken from the actual records of medication administration.

Review of medical records for EKGs, medication administration and outcome of hospitalization

Each chart was reviewed for the completeness of the records of actual medication administration, the availability of standard 12-lead EKGs during the period of intravenous erythromycin administration (here termed exposed EKGs), and the availability of EKGs either before or at least a week after the administration of erythromycin by any route (unexposed EKGs). It was additionally required that patients be in sinus rhythm with heart rates in the range of 50–120 b.p.m. As we had selected against patients with heart disease to limit potential confounding, we anticipated that many of the study subjects would not have multiple standard EKGs in their medical records. In order to be able to include more patients we accepted unexposed EKGs that had not been obtained during the same hospitalization, and some were taken from the hospital's medical records for outpatient visits. Appropriate pairs of exposed and unexposed 12-lead EKGs were found in the medical records of 17/50 (34%) patients. We took all available EKGs for each patient so that the actual number of EKGs per patient ranged from a minimum of two to a maximum of six, and a total of 57 relevant EKGs were identified in the charts of these 17 patients. Multiple duplicate copies were made of the 57 study EKGs on the same copy machine.

Selection and measurement of individual beats on EKGs

We selected specific leads and beats to measure. One beat was marked for measurement in leads II

and V2 for each EKG. Lead II was chosen as the standard lead for QT measurement because this is the lead in which it is generally easiest to separate T waves and U waves.[12] The QT intervals in lead V2 were measured as well because some think QT intervals should be measured in the lead where they appear to be longest, which is generally an early precordial lead.[13] Beats were marked for reading so that each reader measured the QT interval on the same beat and beats were selected that had a clear RR interval measurable from the preceding beat in order to allow correction of measured QT intervals for rate. Beats were selected for reading by an author blinded to exposure status.

These EKGs were then read independently by two board-certified internists who were blind to the exposure status of the patients at the time of each EKG. The two readers independently agreed that 50/57 EKGs were of sufficient quality to allow measurement of QT intervals in lead II and 49/57 in lead V2. Excluding some EKGs as effectively unreadable resulted in a reduction of the number of patients with paired readable EKGs to 15 for lead II and 14 for lead V2.

Method for measuring QT intervals

Using EKG calipers the readers measured the interval from the earliest deflection of the QRS complex to the end of the T wave for the specified beats. The end of the T wave was determined as the point where the tangent from the steepest part of the final (usually down) slope of the T wave crossed the isoelectric point.[13,14] In the five instances where differences between two readers in the measured QT intervals for a beat exceeded 0.04 s the differences were resolved using readings of a third board-certified internist. The distributions of the 50 sets of differences in measured QT intervals for lead II and 49 sets for lead V2 between the two readers were symmetrical about zero, indicating no systematic differences in measuring between readers.

Calculation of average and corrected QT intervals

The average value of the QT intervals obtained by the two readers were utilized in all subsequent calculations. Corrected QT intervals (QT_c) were also calculated for each individual beat. Many different methods of correcting QT intervals, including methods with single and multiple parameters, have been suggested. The single parameter square root and cube root corrections described below were used, including the RR intervals from the immediately preceding beats.[13]

$$\text{Square root } QT_c = QT/(RR)^{1/2}$$

$$\text{Cube root } QT_c = QT/(RR)^{1/3}$$

Patients had between one and three EKGs available from the periods when they were unexposed and also from the periods when they were exposed to erythromycin. In order to give equal weight to each patient the average corrected QT_c intervals for unexposed and exposed EKGs were found for each patient and used so that each patient had single average values for the corrected QT intervals for leads II and V2 in the unexposed and exposed time periods.

Prolongations in QT_c intervals were calculated by subtracting the average QT_c interval for each individual patient during the period when they were unexposed from the average QT_c interval when they were exposed to intravenous erythromycin. These paired differences were tested against the null hypothesis of no difference using a paired *t*-test.[15] Our *t*-tests were conservative since the 15 paired differences were computed from 50 EKGs.

QT_c intervals were investigated separately for patients who did or did not have pneumonia during the periods when their erythromycin unexposed EKGs were obtained in order to investigate potential effect modification of the erythromycin effect by pneumonia.

RESULTS

Study population

The mean age $\pm$ SE of the 15 study patients was 62.8 ± 5.7 years (median 65 years, range 27–91 years). Seven were male and eight female. The daily dose of intravenous erythromycin was 4 g/day for 11 patients and 2 g/day for the other four. The average duration of intravenous erythromycin therapy at the time of the exposed EKG was 5.5 ± 1.6 days (median 5 days, range 1–25 days), and the average interval between unexposed and exposed EKGs on the same patients was 97 ± 41 days (median 7 days, range 1–485 days).

Heart rates computed from the measured RR intervals ranged from 55–118 b.p.m. No patient was documented to have an episode of ventricular tachycardia. One 72-year-old female patient expired after life support was withdrawn.

Table 1 — Mean values and ranges of uncorrected and corrected QT intervals measured in lead II of EKGs obtained from the 15 patients when they were unexposed to erythromycin

	QT intervals	
	Mean (s)	Range (s)
QT interval uncorrected	0.360	(0.315–0.415)
QT_c interval corrected square root RR	0.422	(0.374–0.505)
QT_c interval corrected cube root RR	0.399	(0.362–0.471)

Concomitant drug administration

None of the study subjects received any antiarrhythmic agents, astemizole, terfenadine or chloral hydrate during the study. Three of the study subjects received digitalis throughout the study period (during both unexposed and exposed EKGs), and one received trimethoprim sulfamethoxazole throughout the study period.

QT interval in lead II

The mean QT_c interval (lead II, square root RR correction) was 0.422 s in the absence of erythromycin (Table 1, Fig. 1). The means and ranges for the QT_c intervals among the unexposed are almost identical to those obtained from adults in the Framingham Study.[16] In contrast, the mean QT_c interval (lead II, square root RR correction) was 0.467 s in the presence of erythromycin (Fig. 1). The administration of erythromycin increased the mean QT interval from the normal to the abnormal range. Without erythromycin three of the 15 study patients had mean QT_c intervals exceeding 0.440 s, which is considered to be the upper limit of the normal range. During erythromycin administration nine of the 15 had mean QT_c intervals exceeding 0.440 s (Fig. 1).

The average prolongation of the QT_c interval (lead II, square root RR correction) was 0.045 s $P < 0.01$ (Table 2). This prolongation of the QT_c interval with intravenous erythromycin measured in a clinical setting is almost identical with the prolongation of 0.042 s found in an experimental setting.[8]

Potential modifying effect of clinical pneumonia

Although all 15 patients had clinical pneumonia when the erythromycin exposed QT intervals were measured, this was the case for only 11 of the patients when unexposed intervals were measured. The QT intervals on the remaining four patients were obtained when no clinical pneumonia was

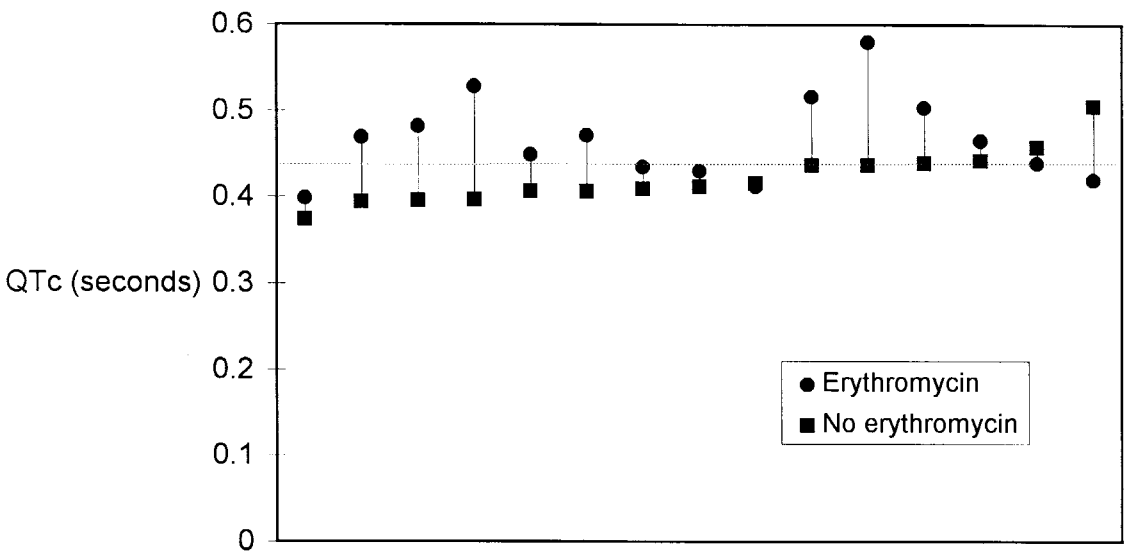

Fig. 1 — Erythromycin effect on QT_c intervals. Average QT_c (lead II, square root correction) are shown for each patient. Values obtained in the absence of erythromycin are shown as squares: those with erythromycin appear as circles. The symbols overlap for patients whose two values are similar. The dotted line at 0.44 s is the upper limit of normal

Table 2 — Mean values and ranges of prolongations of uncorrected and corrected QT intervals measured in lead II of EKGs obtained from the 15 patients when they were receiving intravenous erythromycin

	Prolongation of QT intervals	
	Mean (s)	Range (s)
QT prolongation uncorrected	0.038*	(−0.085 to 0.153)
QT_c prolongation corrected square root RR	0.045†	(−0.085 to 0.143)
QT_c prolongation corrected cube root RR	0.043‡	(−0.086 to 0.148)

*$P < 0.05$; †$P < 0.01$; ‡$P < 0.025$.

present, either before or after the hospitalization for pneumonia. The mean QT_c interval (lead II, square root RR correction) for the four patients whose unexposed EKGs were obtained in the absence of pneumonia was 0.410 s, while the corresponding mean QT_c for the 11 patients whose unexposed EKG was taken during the episode of clinical pneumonia was 0.426 s, or 0.016 s longer ($P =$ ns). This 0.016-s difference in the unexposed QT_c associated with pneumonia is small compared with the 0.045-s prolongation in QT_c associated with erythromycin exposure, indicating that clinical pneumonia did not cause the observed increase and that pneumonia did not significantly modify the erythromycin effect.

Parallel analysis of data for lead V2

We conducted a parallel analysis of results based on the data for QT_c intervals among the 14 patients with paired measurements in lead V2 with the square root RR correction with similar results. The mean erythromycin unexposed QT_c (lead V2, square root RR correction) was 0.420 s and the QT_c interval during the erythromycin exposed period was 0.450 s. As a result the erythromycin-associated QT_c prolongation was smaller, 0.030 s ($P < 0.025$). However, the erythromycin exposure again moved the mean QT_c from the normal to the abnormal range.

DISCUSSION

In this study we have demonstrated a substantial prolongation of the QT_c interval associated with administration of intravenous erythromycin among patients hospitalized for simple pneumonia. While erythromycin was administered, the mean QT_c interval actually moved from the normal into the abnormal range, as more than half of the study subjects developed prolonged QT_c intervals.

Antiarrhythmic agents such as quinidine and procainamide have long been known to prolong QT intervals and induce ventricular tachycardia, especially torsades de pointes.[17–19] The mean uncorrected QT interval among patients on these drugs just prior to development of ventricular tachycardia was 0.600 s,[17,18] which is longer than the longest QT intervals observed in this study. Terfenadine, a non-cardiac drug, was systematically evaluated for its effect on the QT_c interval and at the recommended dose was found to prolong the QT_c interval by 0.005–0.015 s.[19] We have documented the effect of erythromycin to be about four times as great.

In laboratory investigations or studies of normal volunteers one need not worry about potential confounding of the erythromycin effect by any diseases or any other medications because all diseases and all other medications can be excluded. However, studies of normal volunteers provide no information on the adverse effects of erythromycin as it is generally used in clinical medicine. There is always the possibility in a retrospective observational study that other factors may have influenced the apparent effect of erythromycin.

On reading the medical records we found no misclassification of erythromycin exposure or EKGs. However, patients receiving erythromycin therapy for infectious diseases usually have multiple diagnoses and receive a multiplicity of other medications, so in order to obtain clinically useful information, epidemiologists must anticipate possible confounding and effect modification. In this study we limited potential confounding by having each individual serve as his or her own reference, by restricting consideration to patients with simple pneumonia as the primary diagnosis, and further excluding those who received common antiarrythmics known to affect the QT_c interval. By selecting against patients with heart disease in order to avoid confounding, it was inevitable that standard 12-lead EKGs would be relatively rare

among our remaining study subjects. To increase the number of study subjects we accepted unexposed EKGs from outpatient clinic visits as well as those taken during admission. As a result, electrolytes were not available in association with EKGs obtained from outpatients, so that we could not uniformly record electrolyte levels in relation to every EKG.

In order for our observed substantial clinical effect to be the result of confounding by changes in electrolyte levels, for example, rather than the simple effect of erythromycin, one would have to assume that for each of the study patients electrolytes changed in concert with erythromycin administration. This would mean that for the patients who had the unexposed EKG after erythromycin the electrolytes would have to change in the opposite direction temporally from the other patients who had the unexposed EKG before erythromycin. It would have been an extraordinary coincidence for electrolytes to have changes in these longitudinally opposite directions in these two subgroups of patients. It is far more likely that erythromycin simply prolongs the QT_c interval in a clinical setting, and for the majority of our study patients erythromycin changed a normal QT_c interval into an abnormal one.

We are, however, concerned about possible selection bias, as selection of patients into this study depended on underlying disease and the past actions of their physicians. All of our study subjects had clinical pneumonia, and in addition, insofar as the availability of suitable paired 12-lead EKGs was a requirement for entry into the study, this criterion may have selected a non-representative subset of patients with pneumonia.

In spite of our selection of study patients from the DRGs including only simple pneumonia and our additional requirements that they not be receiving antiarrhythmic agents and be in sinus rhythm, it is possible that more EKGs would have been retained in the charts of patients for whom there was evidence of, or concern about, concomitant heart disease. As a result, our study patients may have had more heart disease than others with simple pneumonia. If concomitant heart disease modifies the effect of erythromycin on prolonging the QT_c interval, then our study patients may not represent the effect of erythromycin on other individuals without heart disease. Prolongation of the QT_c interval was not specifically mentioned in the notes in the medical records of any of the study patients.

Our study patients may thus differ in two respects from healthy volunteer subjects in experimental studies, as our subjects all had clinical pneumonia and may have had some tendency toward heart disease as well. The magnitude of the prolongation of 0.045 s found in this clinical setting is similar to the prolongation of 0.042 s observed when erythromycin was administered to healthy volunteers.[8] Although we cannot judge from our data alone what effect this selection may have had on the outcome of our investigation, the concordance of our results with those obtained from studies in experimental settings suggests that erythromycin administration is the major determinant of the observed prolongation of QT_c intervals.

There were no adverse clinical outcomes related to the administration of erythromycin in this small clinical study. However, the erythromycin-induced prolongation of the mean QT_c interval into the abnormal range is cause for concern and suggests that further investigation of the effects of various drugs and illnesses on QT_c intervals should be conducted.

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