Antibiotics and acquired long QT syndrome: advice for the prescriber.

Dr. Richard Kovacs

Case Study: An 85 year old woman was admitted to her local hospital with pneumonia. She had been in good health except for mild hypertension treated with a combination of diuretic and angiotensin receptor blocker. Two years prior she fell and fractured her radius. She underwent an open reduction internal fixation under general anesthetic and did well. On presentation with pneumonia, she appeared ill, with BP 122/78, Pulse 85, Respirations 20 and Temperature 39°C. Lung exam revealed consolidation of the left lower lobe. Her WBC was 20,000. Serum chemistries were normal, including potassium level. Chest X-Ray revealed lower lobe pneumonia on the left. She was started on moxifloxacin 400 mg twice a day. She was placed on oxygen and telemetry monitoring. The next day telemetry monitoring revealed a polymorphic ventricular tachycardia consistent with Torsades de Pointe. Moxifloxacin was discontinued. The patient had no further arrhythmia.

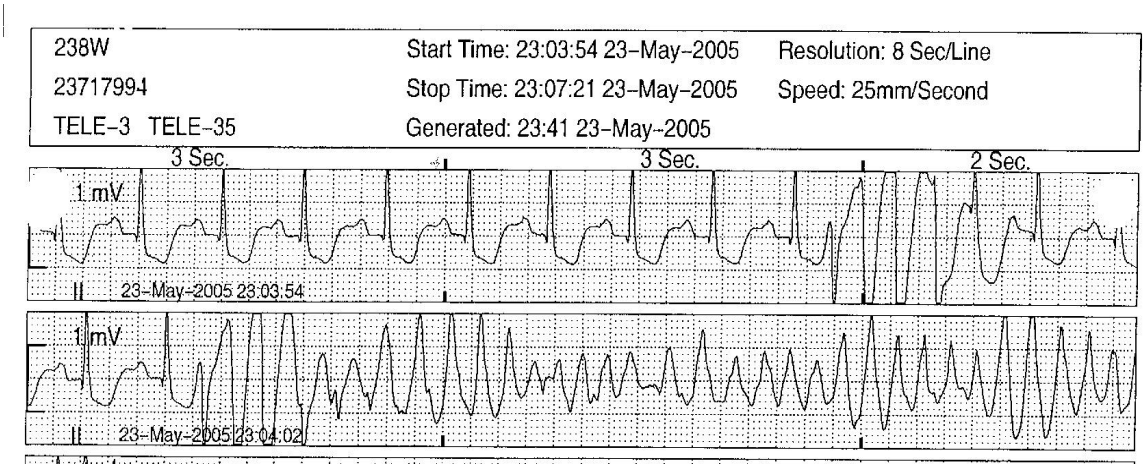


Figure 1. Telemetry monitoring of the patient mentioned above. Marked repolarization abnormalities are seen prior to the onset of Torsades de Pointe.

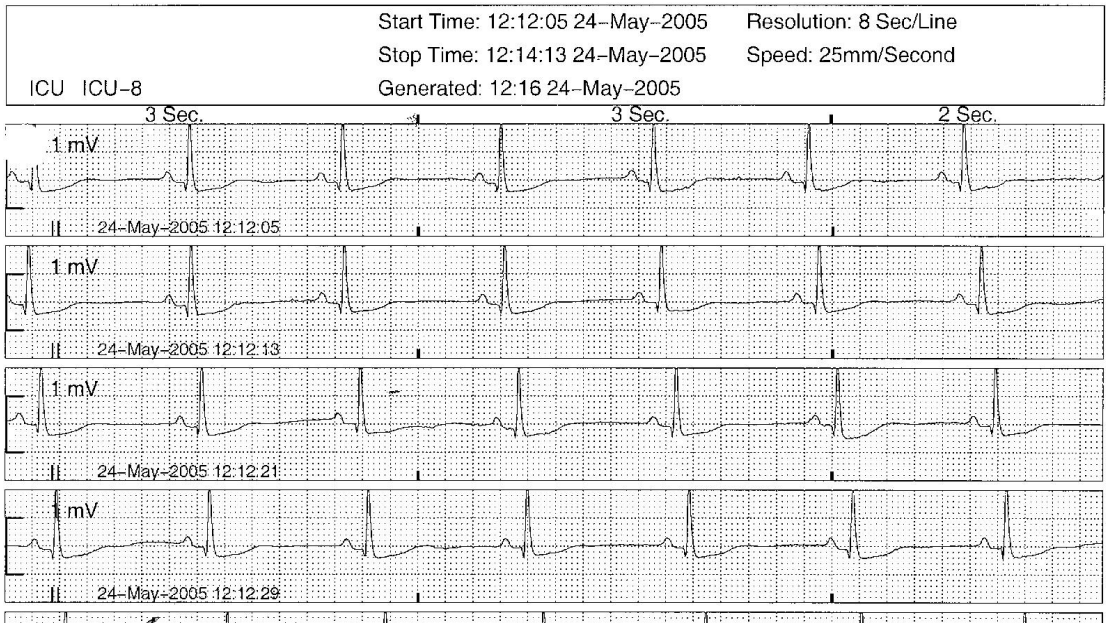


Figure 2. The day following the trace illustrated in Figure 1, there continues to be prominent repolarization abnormalities. The absolute QT interval is difficult to measure in this monitor lead strip, due to the indistinct end of the T wave, but clearly QT is prolonged.

Background:

Evidence has accrued that several non-cardiac drugs may prolong cardiac ventricular repolarization (hence, the QT interval on the surface electrocardiogram) to such a degree that potentially life-threatening ventricular arrhythmias (e.g. torsades de pointes) may occur, especially in case of overdosage or pharmacokinetic interaction. Antibiotics are used frequently in all age groups in hospital and outpatient settings. Antibiotics are used in combination with many cardiac and non-cardiac drugs. All clinicians, generalists and specialists will manage patients taking antibiotics. Therefore, antibiotics that might cause proarrhythmia or interact with other drugs or diseases that predispose to proarrhythmia are a major concern in drug safety.

In the 1960's and 1970's, reports already existed on the cardiotoxicity of some drug classes, such as anti-psychotics and H1 receptor antagonists, but these remained mostly confined to the specialized literature, and the ability of a drug to prolong the QT interval was usually considered a pharmacological curiosity of uncertain significance. Although torsades de pointes can occur in patients with congenital long QT syndrome and is a known risk of many antiarrhythmia drugs. It also is now known to occur as an adverse effect of many non-cardiac drugs.

Antibiotics that have been implicated in acquired QT prolongation as well as clinically important torsades de pointes are listed on websites dedicated to the dissemination of this information to patients and providers (Tables 1-3). These data are largely dependent on spontaneous reporting of adverse events; a system of safety monitoring that will underestimate the incidence of events due to under reporting. One antibiotic (grepafloxacin) was withdrawn from the market. We suspect

multiple other antibiotics have been terminated in development due to a potential for proarrhythmia, but these data are not readily available, due to their proprietary nature. Although drug induced torsades de pointes due to antibiotic administration is relatively rare in the general population (as might be seen by the primary care provider), in our experience, torsades de pointe may occur in as many as 10% of vulnerable patients taking certain non-cardiac drugs at high doses (1). Although the incidence of antibiotic-induced proarrhythmia is much less than 1%, proarrhythmia does occur and should be a drug side effect of concern to the prescriber because of the potential for severe consequences.

Torsades de pointes may also occur as a result of drug interactions due to one of two mechanisms. First a pharmacodynamic interaction can occur between two or more QT-prolonging drugs, the additive effect of which may put the patient at risk even when there is no known interaction between the agents. This potential for a pharmacodynamic interaction, in our opinion, is largely a theoretical concern, without clinical data to substantiate. The potential for an antibiotic with weak HERG blocking activity to interact with, for example, an antiarrhythmic drug with potent HERG activity such as sotalol, will depend on many factors related to the relative affinity of the drugs for the receptor. A factor as simple as heart rate may have profound effects on the relative and/or additive effects of such combinations. Despite this lack of clinical data, warnings to avoid the concomitant use of two QT prolonging drugs appear in US drug labels.

Second, a pharmacokinetic interaction can take place between one or more QT-prolonging drugs and a drug that reduces clearance of the QT-prolonging drug(s), with a subsequent increase in the concentration of the drug (as was the case with the interaction between terfenadine and ketoconazole) (2). This interaction occurs most commonly through inhibition of the cytochrome P450 isoenzymes responsible for the metabolism of some QT-prolonging drugs. Although the risk of TdP is greatest when antiarrhythmic drugs are used (approximately 1%-8%), recent attention has been given to non-cardiac medications that may be prescribed with little or no attention to EKG markers of toxicity. Of the anti-infectives suspected of prolonging the QT (e.g., certain fluoroqunilones, macrolides, azole antifungals, and pentamidine), it has been proposed that macrolides may have the greatest potential for causing QT interval prolongation and/or TdP. Data on the relative risks are sparse, however, as many doses of antibiotics are given in the outpatient setting without EKG monitoring of any type. Spontaneous reporting of adverse events such as syncope or cardiac arrhythmias will underestimate the incidence of arrhythmias and no systematic study of the relative risks of antibiotics is available.

Identification and widespread knowledge of risk factors that may precipitate prolongation of QT interval into life-threatening arrhythmias has become an important issue. This has fostered discussion on the mechanisms underlying proarrhythmic effects shared by apparently disparate classes of drugs, on the clinical relevance of this side-effect and on possible guidelines to be followed by drug companies, ethics committees and regulatory agencies in the risk-benefit assessment of new and licensed drugs. All new antibiotics, in fact all new drugs with significant systemic bioavailability, are to be tested for the potential of the drug to prolong QT (3). This information is appearing in label instructions to the presciber, and warnings to the prescriber and

the patient. Some drugs may not be developed or marketed based on real or perceived risk of torsades de pointe. Given the increasing number of antibiotic resistant pathogens and the need for new antibiotics in the clinic, the risk of proarrhythmia needs to be balanced against the benefits of new antibiotics to public health. Practitioners await clear guidance on the relative risks of various antibiotics, on the risks to individual patients that antibiotic therapy entails, and the risks of combinations of drugs that may prolong QT.

Scope of the Issue:

Data on the global use of antibiotics is not readily available, but considering the use of these drugs in the inpatient and outpatient setting, the use of antibiotics is ubiquitous. Several large databases have provided some estimates of the scope of the issue. Data from a population based study involving a cohort of nearly 5 million outpatients revealed that drugs with QT-prolonging potential, particularly antibiotics, are prescribed and dispensed frequently in the outpatient setting (3). Of the 4.8 million patients, 1.1million filed claims for at least one QT prolonging drug. Of these patients, nearly 47% filled a prescription for either clarithromycin or erythromycin. Furthermore, of these 1.1 million pts, nearly 10% filled overlapping prescriptions for at least one other QT-prolonging drug, or at least one drug that inhibits the clearance of the QT prolonging agent.

Novel epidemiological methods have been used to mine pharmacy databases to investigate particular drugs. Erythromycin is a commonly prescribed medication that was thought to be largely free of serious toxicity. Case reports have suggested that erythromycin is associated with an increase risk of torsades de pointes. Reviews from the FDA adverse drug event reporting system identified 82 reports of torsades de pointes in which erythromycin was mentioned. Confirmatory evidence was however lacking until a study involving nearly 1.2 million patients who were taking oral erythromycin, revealed that that the risk of sudden cardiac death was significantly higher in this cohort (4). Another key finding was that the risk increased to nearly 5 times in the cohort taking both erythromycin and drugs that decrease its metabolism (azoles, calcium channel blockers).

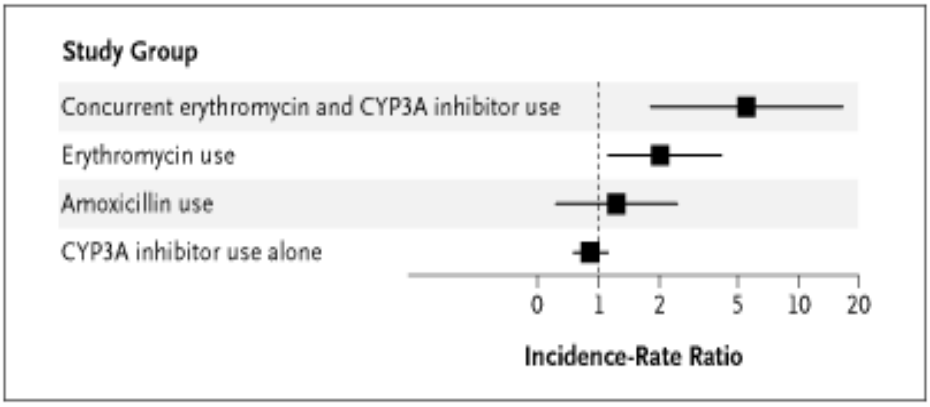


Figure 3. Relative risk of death for patients taking erythromycin and amoxicillin. The concomitant use of erythromycin and a CYP3A inhibitor increased risk for death nearly 5-fold (4)

In contrast, no increase in the risk of sudden cardiac death was seen in patients taking either amoxicillin or amongst former users of erythromycin. This effect of erythromycin may result from blockade of the cardiac potassium channel encoded by the human ether-a-go-go-related gene (HERG).

Another large database was used to compare the relative risk of quinolone antibiotics in the US Veterans Administration Hospitals (5). Data were analyzed from 4.5 years of prescriptions. During this time, 25 cases of torsades de pointes were reported in patients receiving quinolones. From these data, relative risks were assigned to the drugs, with no cases of torsades de pointes reported associated with moxifloxacin use (despite its known ability to prolong the QT interval). 0.3 cases of torsade de pointes per 10 million prescriptions were reported with ciprofloxacin, 5.4 cases per 10 million prescriptions for levofloxacin and 27 cases per 10 million prescriptions for gatifloxacin.

Moxifloxacin has had special attention paid to QT prolongation both pre-approval (in vitro studies suggested an effect on cardiac ventricular repolarization) and post approval. Soon after release, data on more than 2,000,000 patients were reviewed (6), revealing only a single report of torsades de pointes in an elderly woman with cardiac disease and hypokalemia. Moxifloxacin has been felt to be a drug that modestly prolongs QT interval at the usually prescribed doses, but does not pose a risk of torsades de pointes. In fact, most “thorough QT studies” performed to comply with ICH E14 use moxifloxacin (400 mg) as a positive control to prove assay sensitivity in healthy subjects. To date, we are unaware of any instances of torsades de pointes in these trials, and ethics committees have routinely approved the administration of moxifloxacin to these volunteers despite its known effect on the QT interval.

In our own experience, the incidence of marked QT prolongation associated with inpatient antibiotic use may be underestimated. During one recent month (June 2007) we surveyed patients on our inpatient cardiology consult service at an urban teaching hospital. Using a conservative definition of prolonged QT (> 500 msec.), we identified 5 patients with a markedly prolonged QT interval while taking antibiotics. Four of the five patients were female.

Multiple lines of evidence suggest that antibiotic use is associated with a small risk of clinically significant arrhythmias. Events are rare, and the individual practitioner is unlikely to see an event. Even if an event is seen, it may not be recognized as a proarrhythmic effect of the antibiotic, and, in our opinion, is extremely unlikely to be reported to regulatory agencies as an adverse drug effect. Further work is needed to define the risk of proarrhythmia, and give guidance to prescribers.

Table 1. Antibiotics with Risk of Torsades de Pointes:

Generic Name	Brand Name	Class / Clinical Use	Comments
Chloroquine	Arelan®	Anti-malarial / malaria infection	
Clarithromycin	Biaxin®	Antibiotic / bacterial infection	
Erythromycin	E.E.S.®	Antibiotic; GI stimulant / bacterial infection; increase GI motility	Females > Males
Erythromycin	Erythrocin®	Antibiotic; GI stimulant / bacterial infection; increase GI motility	Females > Males
Halofantrine	Halfan®	Anti-malarial / malaria infection	Females > Males
Pentamidine	NebuPent®	Anti-infective / pneumocystis pneumonia	Females > Males
Pentamidine	Pentam®	Anti-infective / pneumocystis pneumonia	Females > Males
Sparfloxacin	Zagam®	Antibiotic / bacterial infection	

Modified from http://torsades.org/medical-pros/drug-lists.

Table 2. Antibiotics with Possible Risk of Torsades de Pointes:

Generic Name	Brand Name	Class / Clinical Use	Comments
Moxifloxacin	Avelox®	Antibiotic / bacterial infection	
Gemifloxacin	Factive®	Antibiotic / bacterial infection	
Ofloxacin	Floxin®	Antibiotic / bacterial infection	
Foscarnet	Foscavir®	Anti-viral / HIV infection	
Telithromycin	Ketek®	Antibiotic / bacterial infection	
Levofloxacin	Levaquin®	Antibiotic / bacterial infection	
Roxithromycin*	Rulide®	Antibiotic / bacterial infection	* Not Available in the United States
Amantadine	Symmetrel®	Dopaminergic / Anti-viral / Anti-infective / Parkinson's Disease	
Gatifloxacin	Tequin®	Antibiotic / bacterial infection	
Voriconazole	VFend®	Anti-fungal / anti-fungal	
Azithromycin	Zithromax®	Antibiotic / bacterial infection	

Modified from http://torsades.org/medical-pros/drug-lists.

Table 3. Antibiotics to be Avoided by Congenital Long QT Patients:

Generic Name	Brand Name	Class / Clinical Use	Comments
Chloroquine	Arelan®	Anti-malarial / malaria infection	
Moxifloxacin	Avelox®	Antibiotic / bacterial infection	
Trimethoprim-Sulfa	Bactrim®	Antibiotic / bacterial infection	
Clarithromycin	Biaxin®	Antibiotic / bacterial infection	
Ciprofloxacin	Cipro®	Antibiotic / bacterial infection	
Fluconazole	Diflucan®	Anti-fungal / fungal infection	
Erythromycin	E.E.S. ®	Antibiotic; GI stimulant / bacterial infection; increase GI motility	Females > Males
Erythromycin	Erythrocin®	Antibiotic; GI stimulant / bacterial infection; increase GI motility	Females > Males
Gemifloxacin	Factive®	Antibiotic / bacterial infection	
Ofloxacin	Floxin®	Antibiotic / bacterial infection	
Foscarnet	Foscavir®	Anti-viral / HIV infection	
Halofantrine	Halfan®	Anti-malarial / malaria infection	Females > Males
Telithromycin	Ketek®	Antibiotic / bacterial infection	
Levofloxacin	Levaquin®	Antibiotic / bacterial infection	
Pentamidine	NebuPent®	Anti-infective / pneumocystis pneumonia	Females > Males
Ketoconazole	Nizoral®	Anti-fungal / fungal infection	
Pentamidine	Pentam®	Anti-infective / pneumocystis pneumonia	Females > Males
Roxithromycin *	Rulide®	Antibiotic / bacterial infection	* Not Available in the United States
Itraconazole	Sporanox®	Anti-fungal / fungal infection	
Trimethoprim-Sulfa	Sulfa®	Antibiotic / bacterial infection	
Amantadine	Symmetrel®	Dopaminergic / anti-viral / anti-infective / Parkinson's Disease	

Voriconazole	VFend®	Anti-fungal / anti-fungal	
Sparfloxacin	Zagam®	Antibiotic / bacterial infection	
Azithromycin	Zithromax®	Antibiotic / bacterial infection	

Modified from http://torsades.org/medical-pros/drug-lists.

Table 4. Antibiotics Unlikely to Cause Torsades de Pointes:

Generic Name	Brand Name	Class / Clinical Use	Comments
Ciprofloxacin	Cipro®	Antibiotic / bacterial infection	
Fluconazole	Diflucan®	Anti-fungal / fungal infection	
Itraconazole	Sporanox®	Anti-fungal / fungal infection	
Ketoconazole	Nizoral®	Anti-fungal / fungal infection	
Trimethoprim-Sulfa	Sulfa®	Antibiotic / bacterial infection	
Trimethoprim-Sulfa	Batrim®	Antibiotic / bacterial infection	

Modified from http://torsades.org/medical-pros/drug-lists.

Considerations for the antibiotic prescriber:

Prescribers face several key issues. First, what are the real hazards associated with administering antibiotics to an individual, and what about drug combinations? Although individual antibiotics do prolong the QT interval, the strength of the evidence regarding the dangers associated with their use, either alone or in combination is not uniform. The incidence of torsades de pointes in an individual may be less than one in ten thousand. The prescriber will not be likely to observe adverse events in the course of usual patient care.

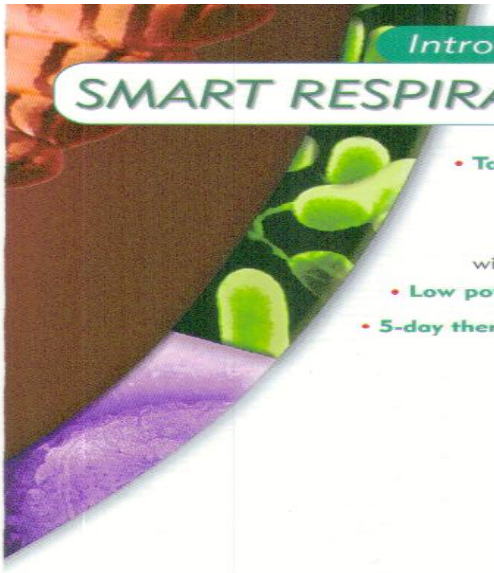
Secondly, it is not known how much risk increases when multiple QT-prolonging drugs are taken over a period of time, or in pts who are felt to be at higher risk for arrhythmias (e.g., elderly, pts with impaired renal clearance, patients with ventricular hypertrophy or dysfunction, patients prone to electrolyte abnormalities and women). Third, multiple physicians may care for a patient and a failure to communicate with other health providers may lead to the prescribing of potentially dangerous drugs or drug combinations.

The prescribing information contained in the drug label is the main source of information available to the prescriber concerning the risk.

Labeling information:

Since the heart is a frequent site of toxicity of pharmaceutical compounds in humans, a thorough preclinical evaluation of possible adverse effects on cardiac structure and function is carried out. The prescriber may not be aware of the strength of the preclinical signal for proarrhythmia based on labeling information alone, and the label may not contain detailed information on this subject. Even prior to candidate drug selection, structure analysis may suggest the potential for a proarrhythmic effect (7). In vitro assays are conducted to determine the effects of the compound and metabolites on cardiac ion channels, (in particular IKr) and prolongation of the QT interval is assessed in vivo animals, and the proarrhythmic risk of the new compound is evaluated by integrating the results of these tests with clinical data, usually from healthy volunteers, but sometimes from patients.. Drug effects on cardiac electrophysiological function may be contained in the clinical pharmacology section of the United States label, for example, a section seldom referenced by the prescriber. Warnings may be “black boxed” for emphasis or simply contained in the label text (figure 3). Post market safety data may not appear in the label for some time, even if a signal is detected from pharmacovigilence monitoring.

Current labeling, at least in the U.S., provides little guidance to the prescriber about the risk of a compound to an individual patient.



Introducing the world's first ketolide

SMART RESPIRATORY COVERAGE...

- **Tailored for common pathogens in*:**
  - AECB
  - Acute bacterial sinusitis
  - Mild to moderate CAP

  with no enteric gram-negative coverage
- **Low potential to induce resistance** to itself in vitro
- **5-day therapy** in AECB and acute bacterial sinusitis*

NEW Ketek®

TELITHROMYCIN | tablets

A Smart Choice

www.KETEK.com

Important Safety Information:

KETEK is contraindicated in patients taking cisapride or pimozide and in patients with a history of hypersensitivity to telithromycin or any macrolide antibiotic. Exacerbations of myasthenia gravis have been reported in patients with myasthenia gravis treated with KETEK. KETEK is not recommended in patients with myasthenia gravis. KETEK has the potential to prolong the QTc interval of the electrocardiogram in some patients. QTc prolongation may lead to an increased risk for ventricular arrhythmias, including torsades de pointes. Thus, KETEK should be avoided in patients with congenital prolongation of the QTc interval, and in patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (eg, quinidine and procainamide) or Class III (eg, dofetilide) antiarrhythmic agents. **KETEK may cause visual disturbances particularly in slowing the ability to accommodate and the ability to release accommodation.** Visual disturbances included blurred vision, difficulty focusing, and diplopia. Hepatic dysfunction, including increased liver enzymes and hepatitis, with or without jaundice, has been reported with the use of KETEK. Caution should be used in patients with a previous history of hepatitis/jaundice associated with the use of KETEK. Use of simvastatin, lovastatin, or atorvastatin concomitantly with KETEK should be avoided. If KETEK is prescribed, therapy with simvastatin, lovastatin, or atorvastatin should be suspended during the course of treatment. Concomitant treatment of KETEK with rifampin, a CYP 3A4 inducer, should be avoided. Most adverse events were mild to moderate and included diarrhea, nausea, headache, dizziness, and vomiting.

Please see brief summary of prescribing information on adjacent page.

Figure 3. An advertisement for telithromycin as it appeared in a US medical journal. The important safety information contained in the small type face includes a contraindication to the administration of telithromycin together with two non-cardiac drugs that also prolong QT (cisapride and pimozide), a fact which may not be obvious to many antibiotic prescribers. The warning also states that telithromycin "should" be avoided in patients with ongoing "proarrhythmic conditions" or patients taking Class IA or Class III anti arrhythmic agents. Telithromycin should also be avoided in patients with congenital long QT syndrome.

Practical Considerations for the Prescriber:

Clinicians need to be aware that some antibiotics may produce clinically significant arrhythmias, and that risk is not uniform across classes or within a class. Labels created after the inception of ICH E14 will have more uniform data on the risk for QT prolongation than labels for older antibiotics. Websites such as torsades.org can be a valuable source of information for prescribers. Prescribers need to be aware of drug-drug interactions or metabolic variants that increase the plasma levels of compounds that block HERG. Patients with cardiac disease and patients taking cardiac medications may be at significantly added risk. Patients with congenital Long QT

Syndromes may be at added risk. Congenital long QT may not be recognized, and even with currently available genotyping, patients may not be sure of their risk.

A baseline electrocardiogram to screen for a prolonged QT, although not practical before every antibiotic prescription, may be warranted in high risk patients: the elderly, patients with manifest heart disease, or those taking concomitant cardiac medications. In those patients with baseline prolonged QT, certainly with QT/QTc > 500 msec, antibiotics with a recognized QT liability should be avoided.

If an antibiotic known to prolong QT must be given in an individual case (no safer options exist), EKG monitoring may be used to mitigate risk, similar to a risk management plan we use in our institution to guide the administration of droperidol, a drug that carries a "black box" warning in the US for QT prolongation and torsades de pointes (9).

Table 4 Risk Factors that may exacerbate the potential for an antibiotic to produce Torsades de Pointes

High doses or rapid administration (especially I.V.)
Metabolic Inhibition
Genetic susceptibility due to detected or undetected genetic polymorphisms
Impaired elimination
Bradycardia
Hypokalemia, hypomagnesemia
Left ventricular hypertrophy
Congestive Heart Failure
Female Gender
Age
Concomitant administration of HERG blocking agent (pharmacodynamic interaction)

Post approval surveillance should be improved by all parties – better reporting of adverse unexpected events by prescribers, and timely information on any change in the risk/benefit ratio of a drug from the manufacturer will help insure improvement in safe administration of needed antibiotics.

Conclusions:

Several antibiotics pose a small, but significant risk for proarrhythmia. Prescribers need to be aware of this risk, and the clinical characteristics of patients that may be at higher risk. In the vast majority of patients, the needed antibiotic can be given safely. Further study is needed to determine the effects of multiple agents, the speed and route of delivery of antibiotics and the effect of various forms of heart disease on risk. All clinicians should report unexpected arrhythmias during antibiotic administration to their responsible regulatory agencies to improve our estimates of risk of a rare but potentially life threatening complication of antibiotic therapy.

References:

1. Tisdale JE, Kovacs R, Mi D, McCabe GP, Cariera BL, Sharma N, Rosman H. Accuracy of Uncorrected vs Corrected QT Interval for Prediction of Drug-Induced *Torsades de Pointes* Associated with Intravenous Haloperidol. Pharmacotherapy, Feb 20071.

2. Honig PK, Worthham DC, Zamani K, Conner DP, Mullin J, Cantilena LR. Terfenedine-ketoconazole interaction. JAMA 1993; 269: 1513-1518.

3. E14: The Clinical Evaluation of QT/QTc Internval Prolongation and Proarrythmic Potential for Non-Antiarrhythmic Drugs. Reviewed at: www.ich.org. Europe Union: Adopted by CHMP May 2005, issued as CHMP/ICH/2/04. Date for coming into operation: November 2005. FDA: Published in the Federal Register, Vol. 70 No. 202; pages 61134-61135; October 20, 2005.

4. Curtis LH, Ostbye T, Sendersky V, Hutchison S, Allen LaPointe NM, Al-Khatib SM, Usdin Yasuda S, Dans PE, Wright A, Califf RM Woosley RL, Schulman KA. Prescription of QT-prolonging drugs in a chort of about 5 million outpatients. Am J Med 2003; 114: 135-141.

5. Ray WA, Murray KT, Meredith S, Narasimhulu SS, Hall K, Stein CM. Oral Erythromycin and the Risk of Suddent Death from Cardiac Causes. N ENgl J Med 2004; 351:1089-96.

6. Frothingham R. Rates of torsades de pointes associated with ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin and moxifloxacin, Pharmacotherapy Dec. 2001 1468-72.

7. Iannini PB, Kubin R, Reiter C, Tillotson, G. Reassuring safety profile of moxifloxacin. Clinical Infectious Disease 2001; 32: 1112-1114.

8. Bhavani S, Nagargadde A, Thawani A, Sridhar V, Chandra N. Substructure-based support vector machine classifiers for prediction of adverse effects in diverse classes of drugs 2006; J Chem Inf Model 46: 2478-2486.

9. Yimcharoen P, Fogel EL, Kovacs RJ, Rosenfeld SH, McLenry L, WSakints JL, Alzami WM, Sherman S, Lehman GA. Droperidol, when used for sedation during ERCP, may prolong the QT interval. Gastrointestinal Endoscopy 63(7):979-985, 2006.