The Cardiac Risks of Noncardiac Medications: Should You Make Formulary Changes?

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Recently, the effects of various drugs on the cardiac QTc interval have merited further clinical investigation. The clinical issue is that QT prolongation is associated with torsade de pointes, which may degenerate into ventricular fibrillation and death. The debate is over how much of a risk this is for an individual patient who is given particular drugs.

Although it has been known for three decades that sudden death can result in psychiatric patients treated with antipsychotic drugs, this has only recently become an issue of great concern. In 1996, a new atypical antipsychotic agent, sertrindole (Serlect®), was rejected by the Food and Drug Administration (FDA) because it prolonged the QTc interval and was associated with 12 sudden, unexplained deaths in clinical trials. Sertindole had been approved in the United Kingdom, but more evidence of associated arrhythmias (including more than 30 unexplained deaths) led to its withdrawal in Europe.

In July 2000, psychiatrists received a “Dear Doctor” letter warning that thioridazine prolongs the QTc interval and was associated with torsade and sudden death; further, a “black box” warning was added to the package insert. Several months later, mesoridazine (a metabolite of thioridazine) was also given a “black box” warning for similar reasons, based on published reports of ventricular tachycardia associated with its use.

THE QT INTERVAL

The QT interval is an indirect measure of the duration of the ventricular action potential (depolarization) and ventricular refractory period (repolarization). It consists of two components, the QRS complex (depolarization of the ventricle) and the QT interval (ventricular repolarization). There can be differences in the rate of torsade, depending on which part of the QT interval is lengthened.

Drugs such as tricyclic antidepressants, which block the sodium channel, slow depolarization, widen the QRS, and prolong the QT interval, are rarely associated with sudden death at therapeutic levels. In contrast, agents that block the rapid potassium rectifier channel, such as thioridazine, are more often associated with sudden death, even in healthy individuals. Without going into the physiology of measuring the phases of the cardiac conduction cycle, it should be noted that the length of the QT interval is dependent on heart rate. The interval shortens with increased rate. Because of this, the QT interval is usually corrected for heart rate and is denoted as QTc. These corrected QTc intervals are often calculated using the formula of Bazett. QTc intervals have considerable interindividual and intraindividual differences, making it difficult to precisely define an upper limit for normal.

The Committee for Proprietary Medicinal Products in Europe suggests a value of 450 msec for men and 470 msec for women. It has also been suggested that QTc intervals of greater than 500 msec should be cause for concern, but these values have been observed in healthy individuals. In general, the QTc interval is longer in women than in men and the interval increases with age. Other factors associated with prolonged QT intervals are hypokalemia, hypomagnesemia and hypocalcemia, the presence of diabetes, hypothyroidism, pituitary insufficiency, cardiomyopathy, recent myocardial infarction, sinus bradycardia (< 50 bpm), recent conversion from atrial fibrillation, and specific drugs.

DRUG CLASSES AND THE QTc INTERVAL

More than 200 pharmaceuticals have been associated with torsade in the spontaneous reporting system of the World Health Organization. Of the 20 most commonly reported drugs, half are cardiovascular agents. The majority of these are antiarrhythmic agents (class Ia: disopyramide, quinidine, procainamide; class Ic: flecainide, propafenone; and class III: amiodarone, dofetilide, ibutilide, sotalol). Many noncardiac drugs have been associated with abnormal QTc prolongation and torsade. However, the true incidence with other drugs is difficult to establish because cardiac monitoring is not usually done in these patients and most reports involve single cases.

In the 1990s, terfenidine and astemizole were associated with proarrhythmic effects, according to information obtained from several large databases. Unfortunately, these databases used end-points of low specificity (e.g., cardiac arrest, syncope) and pooled them with more specific cardiac diagnoses. There were other methodological flaws in these databases, and even though there may be a risk of ventricular arrhythmias with these antihistamines, the risk is low and comparable to that with other available antihistamines or ibuprofen.

The possible proarrhythmic effect of antimicrobials has been known for some time and has led to the withdrawal of, or to recent changes in labeling for, several fluoroquinolones. The FDA database for quinolones contains 37 individual cases of torsade. The rates of torsade for the various quinolones range from 0.3 cases per 10 million prescriptions for ciprofloxacin, 5.4 cases per 10 million for levofloxacin, to 27 per 10 million for gatifloxacin. The macrolides have also
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been associated with torsade; the FDA reports an incidence of 0.8 per 10 million prescriptions for azithromycin, 1.1 per 10 million for erythromycin, and 3.4 per 10 million with clarithromycin.

For years, various antipsychotic and antidepressant drugs have been linked to sudden death. Sudden deaths in patients receiving phenothiazines (e.g., chlorpromazine, thioridazine) or butrophenones (e.g., droperidol, haloperidol) have been commonly reported. All of the currently used antidepressants have been shown either to prolong the QTc interval or to be associated with torsade. When clozapine was introduced, it held promise as an agent that would not cause tardive dyskinesia, that would be more effective than phenothiazines, and that would result in fewer cardiovascular effects. Since then, both clozapine and risperidone have been linked to reports of sudden death. Most recently, the approval of ziprasidone was delayed until specific data on its effects on QTc intervals, in comparison to other antipsychotics, was submitted to the FDA. The submitted data showed greater lengthening of the QTc by ziprasidone than risperidone, olanzapine, and haloperidol but less QTc lengthening than by thioridazine. In December 2001, droperidol received a “black box” warning based on FDA data from its Adverse Events Reporting System. There were approximately 100 cases of cardiovascular events associated with droperidol, including 18 deaths, with six of them associated specifically with prolongation of the QTc interval.

Recent FDA actions to amend labeling of available pharmaceuticals may lead to pressure on institutions to make changes in the medication formularies because of concerns about QTc prolongation from certain drugs. To evaluate these concerns, it is important to keep the following points in mind:

• No medications are universally effective or without adverse effects. Which agents have been used in the past? Were they effective? Have any safety problems been documented in the institution?
• Older drugs do not suddenly become more toxic with time. This is especially true after more than 20 years of use. Are there any compelling clinical reasons to make changes from past agents?
• Patients can be screened for risk factors for QTc prolongation or other adverse effects. Can a system be put in place to identify high-risk patients?
• Large databases are often necessary so that one can make informed decisions, but these collections of case reports are often difficult to evaluate and even more difficult for a cause–effect relationship to be assigned.

If the agents you are currently using are working and not causing problems, it does not make sense to make formulary changes based solely on the potential for risk.