Interactions Involving Drugs That Prolong the QTc Interval

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A large number of drugs, representing diverse pharmacologic classes, including antiarrhythmic drugs and noncardiac drugs, have been implicated in causing prolongation of the QTc interval of the electrocardiogram. Almost all of the noncardiac drugs that cause prolonged QTc intervals do so by blocking the movement of potassium into cardiac cells following depolarization. This inward potassium flux is necessary to produce a normal repolarization of the cardiac cell. Disruption of the normal influx of potassium delays repolarization and can lead to arrhythmias including a type of ventricular tachycardia known as torsade de pointes. We have previously written a general discussion of drug interactions affecting the QTc interval.[1]

Although much has been published regarding individual drug-induced changes in QTc intervals, few studies have assessed the effect of pharmacokinetic or pharmacodynamic interactions with these drugs. One of the early interaction studies with a drug known to prolong QTc intervals involved terfenadine and ketoconazole.[2] When terfenadine at a dose of 60 mg every 12 hours was administered, it produced a mean increase in the QTc from 408 to 416 ms. The addition of ketoconazole caused a further increase in the QTc to 490 ms. Increasing terfenadine concentrations resulted in increasing QTc intervals and risk of arrhythmias.

A different result was noted when several antipsychotic drugs were administered alone and with drugs that inhibited their metabolism.[3] Unlike terfenadine, increased drug concentrations resulting from the coadministration of metabolism inhibitors was not accompanied by an increase in the antipsychotic drug-induced QTc prolongation. Perhaps the concentrations of the antipsychotic drugs were not increased adequately (maximum increase in C_{max} was about 4-fold) by the inhibitors. Alternatively, these studies may indicate that drugs possess very different concentration–response curves for QTc prolongation. Terfenadine may have a steeper curve than the antipsychotic agents studied. Recently, the FDA has been requesting drug developers to do QTc testing over a range of drug concentrations likely to occur during drug use. Only by knowing the effect of increasing drug concentrations on the QTc will practitioners be able to assess the risk of drug-induced arrhythmias with specific drugs.

Pharmacodynamic interactions between drugs that affect potassium influx could produce additive (sum of effects), synergic (> sum), or competitive (< sum) effects on the potassium channel. Based on the large number of drug interaction warnings in clinical decision support systems, it appears that for drugs that have been noted to cause QTc prolongation, combinations are assumed to produce synergic or additive outcomes. A recent study reported the effects of droperidol, ondansetron, and droperidol plus ondansetron or placebo administered intravenously to healthy subjects.[4] QTc values measured prior to drug administration were compared with the maximal change in QTc during the first 30 minutes after drug administration. The effect of droperidol on the QTc was greater than that of ondansetron, 28.6 ms and 21.9 ms, respectively. When both droperidol and ondansetron were coadministered, however, the QTc prolongation was 28 ms. Thus, no additive effect was observed with the combination of the 2 drugs.

This outcome could be explained by considering that the 2 drugs act at the same receptor site on the potassium channel. If so, during concurrent administration, the drugs may be competing for the same binding site. If droperidol is more efficient than ondansetron at binding to the potassium channel receptor, the addition of ondansetron at the doses used in this study may simply be unable to compete and produce no additional effect. In vitro studies of drug combinations have also demonstrated less than additive effects on potassium channels.[5,6]

Pharmacokinetic interactions inhibiting the clearance of QTc prolonging drugs may result in increased effect. The magnitude of the change will depend on a number of variables. Predicting the potential significance of these interactions is difficult as data are lacking. Pharmacodynamic interactions may be even more difficult to predict. If drugs compete for the same binding sites on the potassium channel, however, it is probable that combinations will not produce significantly more change in QTc intervals than would occur with the more potent of the 2 agents used alone. Until studies assessing the risk to patients are completed, patients receiving combinations of drugs reported to prolong the QTc interval should be monitored with electrocardiograms. ■