QT-prolonging drugs: Should they ever be used?

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If the current stringent conditions of bodies that register and control medicines had been in force for decades, many commonly used drugs (from antibiotics and antihistamines to antipsychotics and antiarrhythmics) would never have reached the consumer market. Nowadays, pre-release findings of QT prolongation are likely to scupper early-phase trials and result in the abandonment of experimental drugs. Post-marketing surveillance has identified a number of commonly used drugs either as causing QT prolongation or associated with increased sudden unexpected deaths.[1] Thioridazine (see p. 46 of this issue) is such a drug.[2,3]

The QT interval in the ECG for most part represents the electrical 'recharging' of the cardiac myocytes after their depolarisation which initiates systole. This interval is not a passive resting period for the cells but an active, highly co-ordinated orchestration of numerous transmembranous ion channels that open and close in a specific sequence. A change in activity of these ion channels, due either to a genetic defect resulting in a channelopathy or to 'promiscuity' of the ion channels in allowing various drugs and not only ions to enter the channel, can lead to a marked slowing of repolarisation particularly in the M-cells situated between the epicardial and endocardial myocytes of the ventricular wall.[4] Not only may the QT become prolonged but voltage differences in the different layers of the heart may trigger after-depolarisations, polymorphic ventricular tachycardia, usually described as torsade de pointes, and even the total chaotic rhythm of ventricular fibrillation, the lethal arrhythmia that only defibrillation can reverse. The side-effects of drugs that interfere with ion channels may therefore present with silent ECG abnormalities, palpitations, syncope or sudden death. The study reported in this journal confirms that thioridazine is a drug that can have a significant effect on the ECG.[2,5]

Clearly, the best option would be to avoid all drugs that have the potential for prolonging QT. Unfortunately, this solution is not always possible: the drugs may be highly effective in treating the condition for which they are marketed, the drugs may be the cheaper alternative, or there may be no similar non-QT-lengthening drug available. Furthermore, the arrhythmic complications of the drugs may be rare and may have been missed by pre-release testing and only identified by careful post-marketing surveillance.

Can the side-effects of a QT-prolonging drug be predicted or tested for? ECG evidence of QT prolongation in an individual exposed to the drug, especially if marked, should rule out its use. (A QTc interval of > 500 ms is an arbitrarily determined value and used as a marker of unacceptable risk.) Unfortunately, the corollary of a QT below the upper limit of normal does not indicate safety. The QT is a very variable interval on the ECG and is influenced by heart rate, electrolytes, circulating catecholamine levels and even smoking. Drugs that have been shown in population studies to lengthen the mean QT intervals compared with controls may not significantly prolong the interval on random ECGs of a vulnerable individual or prolong the QT beyond the accepted normal upper limit, and yet still pose a risk of a lethal arrhythmia. Normal physiological QT variability and magnitudes of QT lengthening too small to be measured by the standard ECG may mask the covert, potentially life-threatening, electrophysiological effect of the drug.

Conditions not tested for before the launch of the drugs may increase susceptibility to such a drug. Combination with other agents that may alter metabolism or elimination of the drug could result in marked elevation of drug concentration, competitively blocking more vulnerable ion channels. Various patient conditions that reduce the 'recharging' or repolarisation reserve of cardiac myocytes increase the risk of arrhythmias. These conditions include heart failure and electrolyte abnormalities such as hypokalaemia, which may be the result of diuretic use, diarrhoea or bulimia.[4,6] Interestingly, the finding that sudden death is more frequent among psychiatric patients in general and among those on antipsychotics in particular is not new.[3]

One must be aware that while there are many drugs that may prolong the QT, not all these drugs have been implicated individually in causing any clinical arrhythmia.[1] With these drugs, reassurance of their safety comes from their extensive use over many years and continuing, careful and transparent post-release surveillance. These drugs should, however, still not be used in combination with other QT-prolonging drugs or in vulnerable persons.

Drugs that have been implicated in torsade de pointes and lethal arrhythmias should preferably not be used. The ECG has limited value in guiding their use. Yes, it can show when it is probably dangerous to use such drugs (when QT prolongation occurs), but more importantly, even when apparently normal it can never be interpreted as an indication that their use is safe. Justification for the use of these drugs must be the outcome of a careful calculation of risk versus benefit. Thus, in cardiology, we may knowingly prescribe antiarrhythmic agents with a potential of causing torsade at a risk level 100-fold that of some psychiatric drugs (2 - 4% for sotalol v. 1 in 10 000 for some antipsychotics), when the alternative, off the drugs and untreated, is an even higher risk of unsuppressed lethal arrhythmias.[3,6,7] If a similar benefit can be shown for non-cardiac, QT-prolonging and torsade-implicated drugs, then their use can be condoned. If not, these drugs should be avoided.

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