The recent abrupt withdrawal of grepafloxacin by Glaxo Wellcome, in association with seven possibly associated, sudden cardiac deaths and several cases of torsade de pointes, details of which have not apparently reached the public domain, has again highlighted the phenomenon of quinolone-induced QT prolongation and the potential for associated ventricular tachy-arrhythmias originally described with sparfloxacin. In anticipation of the predatory activity which often characterizes realization of apparent, but often factually unfounded comparative advantage by competitor marketing departments within the pharmaceutical industry, it is pertinent to re-examine the facts.

Quinolone-related torsade de pointes and other malignant ventricular tachy-arrhythmias have been described very rarely and only with sparfloxacin, levofloxacin and, most recently, grepafloxacin. However, during preclinical animal toxicological assessment, all quinolones so far adequately investigated have proved to prolong the QT interval. For grepafloxacin, QT prolongation is observed in both rabbits and dogs after intravenous dosage of 10–30 mg/kg. Comparison of grepafloxacin, gatifloxacin and sparfloxacin in the standard rabbit model shows the latter to have a far greater effect on QT but, although sparfloxacin again had an increased propensity for their induction, all agents could cause ventricular arrhythmias. No animal data appear to be available for levofloxacin, although human cases of torsade de pointes in the USA FDA spontaneous reporting records (11 cases in three million treatments) and a report of polymorphic ventricular tachycardia, suggest that animal data would prove positive. For trovafloxacin, withdrawn because of hepatotoxicity, again no animal data are available but the European CPMP commented on QT prolongation within normal physiological limits. Electrocardiographic studies of moxifloxacin in 1500 patients at baseline and 2 h post-dose on days 3–5 of therapy have indicated a mean prolongation of QTc of 6 ms (± 26 ms) in 9.5% of moxifloxacin-treated patients compared with 9.2% of comparators. However, 6.5% of patients had QTc prolongation at baseline and no arrhythmias or other cardiac events were observed. The extended moxifloxacin clinical trial series (2650 patients with ECGs) shows the frequency of significant QTc changes, using CPMP criteria but in the absence of any clinical effect, to be 2.7% for moxifloxacin, 3.7% for clarithromycin and 2.2% for all other comparators (R. Kubin, Bayer, Leverkusen, Germany; personal communication). Thus, almost every quinolone investigated, however partially, provides some evidence of effects on cardiac conduction and some are associated with ‘clinically significant’ events. It is perhaps the latter phraseology which stimulates controversy as, taken alone, prolongation of the QTc is not a ‘clinical’ event.

The QT interval is that ECG measurement which describes the period between onset of ventricular depolarization and the end of the repolarization process. It varies with heart rate. Prolongation of the rate-corrected QT interval (QTc) is recognized to be associated with various malignant tachy-arrhythmias and specifically with torsade de pointes. Long QT intervals are recognized to be either congenital or acquired, in the latter case frequently associated with...
drug administration. When sufficiently prolonged they may precipitate torsade de pointes which, if transient, may present with syncope and, if not, may cause sudden death.7,8 Drugs associated with long QT syndromes and torsade de pointes include cisapride, anti-arrhythmics (quinidine, sotalol and amiodarone), antihistamines (terfenadine and astemizole), psychotropics (fluoxetine) and antibiotics, notably macrolides, but also co-trimoxazole, imidazoles and certain quinolone-related antimalarial agents. However, neither of two recent large review papers included quinolone antibacterial agents as a potential cause.7,8 Further, against a background experience of ciprofloxacin in over 250 million patients, the reporting rate of possibly associated serious cardiac dysrhythmias was one case per million treatments, compared with three per million for clarithromycin and 14.5 per million for sparfloxacin.12 In addition, despite the intense scrutiny of trovafloxacin which followed early reports of hepatotoxicity, no cardiac episodes appear to have been attributed to that drug.

Thus, despite huge exposure of at-risk populations to quinolones, these antibacterial agents have not generally been recognized as causes of the long QT syndrome, associated symptomatic ventricular tachy-arrhythmias or related fatalities. Data on macrolides, which cause greater QTc prolongation than quinolones, also suggest that clinical effects are rare. For example, a year-long, retrospective, university-based study found QTc prolongation to be common and QT dispersion to double during intravenous erythromycin therapy.13 However, although 39% of patients had moderate to severe hepatic dysfunction and pre-existing hypertensive and ischaemic heart disease, only one (0.4%) of the patients with prolonged QTc developed torsade de pointes.

The sudden withdrawal of grepafloxacin must be viewed in this context. There may be significant differences between quinolones as shown by the large differences between, for example, arrhythmogenic doses of grepafloxacin (10–30 mg/kg) and ciprofloxacin (300 mg/kg).5 Determination of IC50 doses of quinolones for the delayed rectifier potassium current (I\(_{Kr}\)) associated with cardiac repolarization clearly demonstrates sparfloxacin to have the greatest effect, IC50 I\(_{Kr}\) being 0.23 μM compared with 26.5 μM for gatifloxacin and 27.2 μM for grepafloxacin.9 Thus, the increased frequency of serious cardiac events with sparfloxacin has a reproducible means of assessment by a model. Significantly, however, the other two quinolones tested had a lesser but still positive result. However, although there is an increasing risk of malignant arrhythmia with increasing prolongation of the QTc5 and this risk may be suggested by QT dispersion,11 an exact relationship between a critical QTc value and ventricular arrhythmia has not been established. Thus, registration agencies have had little alternative to class labelling of all quinolones to warn of possible untoward effects, especially when these drugs are combined with other agents known to prolong the QT interval in at-risk patients. These would include the elderly, females and those with electrolyte disturbance or pre-existing cardiac disease.

For moxifloxacin, additional clinical trial data have expanded the database to over 6000 patients with no changes in the frequency of adverse drug reactions or the extent or frequency of QT prolongation. The FDA Advisory committee, reviewing development of moxifloxacin commented that such evaluation ‘... might serve as a model for working up a drug that affects the QT interval’.15 More than 1 million patients have now received treatment with moxifloxacin and there has been only a single case of possibly associated torsade de pointes. This event, interpretation of which is confounded by the presence of multiple risk factors, occurred in an 83 year-old female ICU patient with pre-existing hypokalaemia, sick sinus syndrome with cardiac pacemaker and coronary artery disease, also receiving digoxin therapy. Therefore, the cardiac safety profile of moxifloxacin is similar in type and incidence to that of other class members, e.g. ciprofloxacin and levofloxacin, with an established safety record. However, the detailed pre- and post-licensing investigation of moxifloxacin appears not to have applied to other new quinolones, which are generally described as having no clinically significant effects without substantiating data. It is of note that the FDA has applied retrospective labelling to levofloxacin and has requested further studies on other compounds, for example gatifloxacin.

Clearly, use of these potent antimicrobial agents in sick patients may increase the potential likelihood of QT prolongation in predisposed populations. It is therefore essential to identify patients at risk; at present, objective data are lacking. However, as risks from both underlying diseases and from concomitant drugs known to prolong the QT interval are almost certainly cumulative and may even multiply, it would be appropriate to avoid or monitor patients considered to be at higher risk. These might include patients with significant cardiac disease, those receiving anti-arrhythmic agents and agents such as cisapride, and patients with a history of arrhythmia. Although more extreme degrees of QTc prolongation are undoubtedly associated with a risk of torsade de pointes,7,8 such effects appear to be no more common with quinolones than with macrolides and the risk may vary between drugs and with co-risk factors. A blanket moratorium would therefore seem less appropriate than an objective assessment of risk; this is in progress for moxifloxacin and is suggested for other quinolones.

References


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