Quinolone-induced QT interval prolongation: a not-so-unexpected class effect


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Sir,

I read with great interest Dr Peter Ball’s recent leading article on quinolone-induced QT interval prolongation.¹ The author’s “re-examination of the facts” is an admirable effort to discuss recently highlighted fluoroquinolone safety issues. While agreeing that well-studied, and generally safe, antibiotics should be used for the treatment of infections, regardless of minor QT prolongation effects, I do not agree that this cardiac effect is established as a fluoroquinolone drug class effect, and would like to offer additional data related to levofloxacin.

Animal safety data on the cardiovascular effect of levofloxacin are available, as shown by Adamantidis and colleagues,² who evaluated the effect of ofloxacin, levofloxacin and sparfloxacin on cardiac repolarization in rabbit Purkinje fibres. These data demonstrated that ofloxacin and levofloxacin did not alter the action potential parameters and, in particular, did not prolong repolarization, at concentrations ranging from 1 to 100 μM. (Typical mean plasma levofloxacin concentrations in humans, after multiple oral doses, range from 5 to 8 μM.³) Sparfloxacin, on the other hand, did lengthen the duration of repolarization in a concentration-dependent fashion beginning at a concentration of 10 μM.² These findings are now supported by additional comparative work in animals involving levofloxacin and other fluoroquinolones. In experiments with isolated guinea pig right ventricular myocardia, sparfloxacin, grepafloxacin, moxifloxacin and gatifloxacin, at concentrations of 100 μM, prolonged the action potential duration at 90% and 50% repolarization (APD₉₀ and APD₅₀) by approximately 40, 25, 25 and 13%, respectively. In contrast, ciprofloxacin (3.3%), trovafloxacin (2.9%), sitafloxacin (2.4%) and levofloxacin (0.6%) had virtually no effect on either APD₉₀ or APD₅₀ as compared with vehicles (−6.1 to 5.2%). Further work in conscious dogs with chronic complete atrioventricular block assessed the proarhythmic properties of levofloxacin and sparfloxacin by Holter ECG monitoring. Whereas high doses of sparfloxacin (60 mg/kg) induced torsades de pointes leading to ventricular fibrillation in all animals, levofloxacin in doses of ≤60 mg/kg did not. These studies are completed and the manuscripts are currently under review for publication. Additionally, blockade of the human cardiac K⁺ channel known as HERG has been implicated as a mechanism underlying most cases of drug-induced long QT syndrome. A recent study demonstrates that levofloxacin has little affinity for this channel (IC₅₀ c. 1 mM) while sparfloxacin is approximately 100-fold more potent. Levofloxacin blockade of other human cardiac K⁺ channels, such as KvLQT1/miniK (IKs), occurs with even lower affinity (D. Rampe, Aventis Pharmaceuticals, personal communication).

The large population exposed to levofloxacin—approximately 15 million prescriptions in the USA—from January 1997 to March 2000 provides reassuring post-marketing safety data on use in ‘real world’ patients. Reporting rates of cardiovascular adverse events, as submitted to the R. W. Johnson Pharmaceutical Research Institute and Ortho-McNeil Pharmaceutical during that period, are extremely low, with less than one case of QT prolongation or torsades de pointes per million prescriptions regardless of whether or not the condition was attributed to underlying disease or concomitant therapy. This is consistent with levofloxacin postmarketing experience data presented by the United States Food and Drug Administration (FDA). During the first 2 years of marketing in the USA, the reporting rate of ventricular arrhythmia and cardiac arrest associated with levofloxacin use was 1.5 per million, as adjusted for secular trend. These FDA data included a broader variety of cardiovascular adverse events and, accordingly, are not specific for torsades de pointes and QT prolongation.¹ ⁴

Finally, Dr Ball infers, from FDA-applied retrospective labelling for levofloxacin, that QT prolongation is characteristic of the entire fluoroquinolone class. Class labelling is not, however, in effect for quinolone-induced QT prolongation, as can be confirmed by a brief comparative review of fluoroquinolone package inserts. Specifically, the revised levofloxacin US labelling⁵ indicates that, ‘During postmarketing surveillance, extremely rare cases of torsades de pointes have been reported in patients taking levofloxacin. These reports generally involve patients with other concurrent medical conditions and the relationship to levofloxacin has not been established.’ We believe these data more accurately reflect the current state of knowledge on levo-
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toxacin and QT prolongation and will allow the reader to make more informed and accurate clinical decisions.

References


