The degree of potassium channel blockade and the risk of torsade de pointes: the truth, nothing but the truth, but not the whole truth

Sami Viskin* and Uri Rosovski

Department of Cardiology, Tel-Aviv Sourasky Medical Center and Sackler School of Medicine, Tel Aviv University, Weizman 6, Tel Aviv 64239, Israel

Online publish-ahead-of-print 15 February 2005

This editorial refers to 'Anti-HERG activity and the risk of drug-induced arrhythmias and sudden death'† by M.L. De Bruin et al., on page 590

Several anti-arrhythmic drugs, as well as medications not intended for cardiac indications, block a specific potassium channel named \( I_{Kr} \) (the rapid delayed rectifying potassium current). In the case of the anti-arrhythmic drugs, \( I_{Kr} \) channels are purposely targeted. By blocking potassium outflow currents, the anti-arrhythmic drugs prolong the action potential. This action (depicted in the electrocardiogram as prolongation of the QT interval) can be advantageous given that prolongation of the action potential also lengthens the refractory period, thereby suppressing common arrhythmias. Unfortunately, by a mechanism explained elsewhere,\(^1\) \( I_{Kr} \) blockade may lead to excessive QT prolongation and trigger a polymorphic ventricular tachyarrhythmia (torsade de pointes) that may degenerate into ventricular fibrillation. Furthermore, because of its unique three-dimensional characteristics,\(^2\) \( I_{Kr} \) channels are very easily blocked by the small molecules of numerous non-cardiac drugs. The result is that otherwise harmless and valuable drugs, like the non-sedative anti-histamines and the quinolone-antibiotics, become potentially lethal pro-arrhythmic medications.\(^3\)

An important study by De Bruin et al.\(^4\) suggests that a strong correlation exists between the strength of \( I_{Kr} \) blockade caused by a given drug and its pro-arrhythmic potential. The concept that stronger \( I_{Kr} \) blockers will lead not only to more QT prolongation but also to higher arrhythmic risk is so logical that the reader will be left wondering why this study was ever conducted, let alone published. In reality, however, this concept has been difficult to prove.\(^5\) Amiodarone, ranolazine, and verapamil illustrate that the correlation between \( I_{Kr} \) blockade and arrhythmogenic potential is not simple. All these drugs are strong \( I_{Kr} \) blockers, yet torsade de pointes is rarely caused by amiodarone,\(^6\) has not been associated with ranolazine,\(^7\) and may even be prevented by verapamil.\(^8\)

De Bruin et al. reasoned that drugs which block \( I_{Kr} \) at concentrations that approximate the concentrations needed to achieve therapeutic effects, would be more likely to be involved in arrhythmic events than drugs with a higher therapeutic-to-toxic ratio. The ideal way of conducting such a study would be to correlate drug-potency (in terms of \( I_{Kr} \) blockade) with the actual incidence of arrhythmic events (i.e. with the percentage of patients who developed arrhythmias among all those receiving the drug). However, drug-induced torsade de pointes is so rare (less than 1:10 000 for drugs with no cardiac indications)\(^3\) that collecting such data for numerous drugs would be a monumental project. Instead, the authors scrutinized a large database of drug-induced adverse events and showed that stronger \( I_{Kr} \) blockers were more likely to cause arrhythmic (as opposed to non-arrhythmic) adverse events. Specifically, the authors first retrieved data from published studies on more than 50 drugs that have \( I_{Kr} \) blocking capabilities. For each drug, the therapeutic drug levels (according to clinical trials) and the drug concentrations expected to block 50% of \( I_{Kr} \) channels (according to in vitro studies) were noted. They then looked at the drug-related adverse events reported and estimated the ratio of ‘arrhythmic events’ (cardiac arrest, torsade de pointes, etc.) to non-arrhythmic events (hepatitis, skin reactions, etc.) for each drug. As projected, reported adverse events for drugs with a high index of \( I_{Kr} \) blockade more commonly involved arrhythmic events, whereas drugs that block \( I_{Kr} \) channels only at concentrations that are...
much higher than those achieved during therapeutic use were implicated primarily in non-arrhythmic side-effects.4 Every stage in the model of De Bruin has important limitations. First, the drug concentrations required to achieve significant IKr blockade (the concentrations needed to block 50% of IKr) were determined in studies that used dissimilar methodology. Drug effects on IKr currents are at times measured in ventricular myocyte preparations from different species (guinea pigs, rabbits, or dogs) or may be tested in non-mammalian cells made to express human IKr channels by transfection with human DNA.5 The drug concentrations needed to achieve IKr blockade in the different preparations may vary by an order of magnitude. Yet, correction for these differences was not attempted in the study of De Bruin.4 Secondly, the therapeutic drug levels selected for the different drugs were derived from a range of clinical trials involving patients who were not necessarily similar (in terms of co-morbidities, concomitant drug administration, etc.) to the patients included in the study of De Bruin. Finally, to gain information about the pro-arrhythmic effects of the drugs included in the study, the authors analyzed the data reported to the International Drug Monitoring Program of the WHO. Although this is a very large database (more than 280 000 adverse event reports were analysed), it represents only a small portion of the drug-induced side-effects that occur in ‘real life’. This is because only a minority of side-effects are ever reported. Moreover, as we do not know why some adverse drug reactions are reported while others are not, the potential for selection bias is considerable. Even the adverse events that are ultimately reported differ in terms of the ‘cause and effect’ relation between the drug and the event (as perceived by the reporting physician). These reports include descriptions of events that are ‘probably unrelated’, ‘possibly related’, or ‘definitively related’ to a given medication. Yet, corrections for the degree of certainty of the ‘drug reaction’ were not made by the De Bruin study.

One should note, however, that all the limitations mentioned earlier probably affected all the medications analysed in this study in a similar manner. In other words, the bias that certainly existed is likely to have played a similar role for all studied medications. On the other hand, one can learn from the drugs which least played a similar role for all studied medications. On the whole, it appears that the potency of a given drug (the relation between the concentrations needed to block IKr channels and those needed to achieve therapeutic effects) should be viewed as a crude predictor of its pro-arrhythmic potential. This information is important for the scientists developing medications, for the physicians prescribing them, and for the patients ultimately consuming them. The association found by De Bruin is probably true, but is not the whole truth. Clinical factors and concomitant medications play a crucial role in arrhythmic events. Indeed, the majority of patients who develop torsade de pointes from non-cardiac medications have clinical characteristics that are easily identifiable prior to drug administration.9 The odds of provoking torsade de pointes with non-cardiac medications are small in the first place and can be further reduced by avoiding their administration to patients with ‘high-risk’ characteristics and, above all, by avoiding drug combinations that increase the risk through drug interactions.9

References