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

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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 IKr (the rapid delayed rectifying potassium current). In the case of the anti-arrhythmic drugs, IKr 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 IKr 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 IKr 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 IKr blockade caused by a given drug and its pro-arrhythmic potential. The concept that stronger IKr 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 IKr blockade and arrhythmogenic potential is not simple. All these drugs are strong IKr 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 IKr 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 IKr 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 IKr 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 IKr blocking capabilities. For each drug, the therapeutic drug levels (according to clinical trials) and the drug concentrations expected to block 50% of IKr 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 IKr blockade more commonly involved arrhythmic events, whereas drugs that block IKr 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 $I_{Kr}$ blockade (the concentrations needed to block 50% of $I_{Kr}$) were determined in studies that used dissimilar methodology. Drug effects on $I_{Kr}$ 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 $I_{Kr}$ channels by transfection with human DNA.5 The drug concentrations needed to achieve $I_{Kr}$ 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 analysed 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 'definitely 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 followed the predicted pattern (see Figure 3 in the article by De Bruin)4 that there are also limitations affecting different drugs in dissimilar ways. For example, the disproportional excess of arrhythmic events reported for ibutilide probably relates to the fact that ibutilide is a short-acting intravenous drug. In contrast to other drugs analysed in this study, ibutilide is always given during continuous electrophysiographic monitoring and this close monitoring facilitates detection of asymptomatic arrhythmias that would otherwise go unnoticed. Also, in the model of De Bruin, medications that are highly pro-arrhythmic but have non-cardiac side-effects even more frequently, would appear to be 'less pro-arrhythmic' than medications that only rarely cause arrhythmias as their only side effect. Perhaps this explains the relatively 'safe' representation obtained for mefloquine and ketoconazole in this study. Finally, 'cardiac arrest' and 'sudden death', terms used to define 'arrhythmic adverse events' may be caused by mechanisms completely unrelated to QT prolongation in patients with organic heart disease. Consequently, medications that are more commonly given to patients with organic heart disease are more likely to be included in reports concerning sudden death. This could explain the verapamil paradox: in the model of De Bruin, verapamil appears to be 'as pro-arrhythmic as haloperidol'. In contrast, the literature on drug-induced torsade de pointes reveals numerous reports of torsade induced by haloperidol6 but (to our knowledge) no reports of torsade de pointes clearly related to verapamil.

The results of the study by De Bruin are remarkable, but so are its limitations. On the whole, it appears that the potency of a given drug (the relation between the concentrations needed to block $I_{Kr}$ 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