Electrophysiological perspectives – what has ranolazine taught us?

Stuart Cobbe*
Walton Professor of Medical Cardiology, University of Glasgow, UK

Effect of ranolazine on QT interval

As an anti-anginal agent, ranolazine has a unique pharmacodynamic profile in that its effects do not depend on changes in heart rate and blood pressure, offering the prospect of combination with agents that have haemodynamic effects. Treatment with ranolazine has been shown to cause modest prolongation of the QT interval by 2–5 ms; however, no cases of torsade de pointes have been seen in clinical trials representing over 1700 patient-years.

Does QT prolongation necessarily predict torsade de pointes?

The phenomena of drug-induced QT prolongation and torsade de pointes can be dissociated in humans and in animals. In a canine model of complete atrioventricular block, drugs that prolong the QT interval to a similar extent show very different incidences of torsade de pointes. For example, d-sotalol and dofetilide both prolonged the QT interval by 45–55 ms, but d-sotalol had an incidence of torsade de pointes of 0–5% compared with 67% for dofetilide.

The QT interval of the surface ECG is a composite of the action-potential duration from all ventricular cells. Action-potential duration and the QT interval are determined largely by the repolarisation process, which is a balance between inward depolarising and outward repolarising currents. Drugs that prolong the action potential and the QT interval may do so by reducing net repolarising potassium currents (e.g. $I_{\text{Kr}}$) or by increasing depolarising sodium ($I_{\text{Na}}$) and calcium ($I_{\text{Ca}}$) currents.

The electrophysiological markers associated with drug-induced torsade de pointes include: prolonged action-potential duration; early afterdepolarisations (EADs) leading to ectopic beats; and increased spatial dispersion of ventricular repolarisation, thus creating the conditions for re-entry. Thus, the mechanism of action of drug-induced torsade de pointes can be viewed as the generation of a trigger and a substrate, both of which result from the increase in action-potential duration.

The trigger is represented by the induction of EADs leading to ectopic beats (extrasystoles), which act as the initiating beats for torsade de pointes. Inhibition of $I_{\text{Kr}}$ prolongs the action potential, and reactivation of inward currents ($I_{\text{Na}}$ and $I_{\text{Ca}}$) elicits EADs that may generate ectopic beats.

The substrate is provided by increased transmural dispersion of ventricular repolarisation (a mechanism for arrhythmias). Drugs that inhibit $I_{\text{Kr}}$, such as d-sotalol, have been shown in a transmural wedge preparation to cause greater prolongation of action potentials in the mid-myocardium than in the epicardium or endocardium, thus increasing dispersion above the normal heterogeneity seen (59 ms dispersion).

In order to cause torsade de pointes, a drug that prolongs action-potential duration and the QT interval must also both induce EADs and increase transmural dispersion of ventricular repolarisation. Drugs that prolong action-potential duration but do not produce...
Fig. 1. Effects of ranolazine on ion-channel currents in canine left-ventricular myocytes, highlighting the overlap between inhibition of $I_{Kr}$ and late $I_{Na}$ at clinically relevant therapeutic concentrations. Adapted from Shimizu et al. 1999 with permission from author and publisher.

these additional electrophysiological effects are not associated with torsade de pointes.

Effects of ranolazine on ventricular repolarisation

Studies to determine the pro-arrhythmic risk associated with ranolazine have investigated the effect of the drug on ion currents, action-potential duration, induction of EADs, and dispersion of ventricular repolarisation. These studies were carried out in a variety of models and in a range of conditions known to increase the risk of torsade de pointes.

Ranolazine has two main effects on ion-channel currents. It inhibits the outward $I_{Kr}$ with an $IC_{50}$ of $12 \mu M$ which tends to lengthen the QT interval. However, ranolazine’s inhibition of the inward late $I_{Na}$ ($IC_{50} \approx 6 \mu M$) mitigates the former effect by tending to shorten the QT interval. The overlap between ranolazine’s inhibition of $I_{Kr}$ and of late $I_{Na}$ occurs within the range of therapeutic concentrations of ranolazine (2–6 $\mu M$), suggesting that the drug’s blocking effect on the outward repolarising current is counterbalanced by its inhibition of the inward current (Fig. 1).

Ranolazine prolongs the action-potential duration, and hence the QT interval, but this effect is not heart-rate dependent. $I_{Kr}$ blockers such as E-4031 or dofetilide cause a much greater prolongation of the action potential at slower heart rates than at faster ones, whereas ranolazine causes the same prolongation at slow and fast rates. This means that prolongation of the QT interval by ranolazine would not be exaggerated during bradycardia.

Experiments in a wide range of models and conditions, and over a broad concentration range (1–300 $\mu M$), have shown that ranolazine does not induce EADs. In fact, it can reverse the action-potential prolongation and suppress the EADs and ventricular tachycardia induced by other agents, such as the $I_{Kr}$ blockers d-sotalol and E-4031 and the late-$I_{Na}$ enhancer ATX-II (Fig. 2). This effect has been shown in Purkinje fibres, cardiomyocytes and whole rabbit hearts.

Ranolazine at concentrations up to 100 $\mu M$ has been shown not to increase dispersion of repolarisation across the left-ventricular wall (transmural dispersion) in a canine wedge preparation (Fig. 3). In addition, no increase in dispersion was seen with ranolazine during...
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hypokalaemia, a condition known to be a risk factor for torsade de pointes.

Conclusion

Because ranolazine neither induces EADs nor increases transmural dispersion, it would not be expected to lead to torsade de pointes, as has indeed been found to be the case in clinical studies. This is in contrast to many other agents that prolong the QT interval and do cause torsade de pointes (Table 1). In fact, ranolazine suppresses the pro-arrhythmic effects of these drugs.

Table 1

<table>
<thead>
<tr>
<th>Drug</th>
<th>Induces EADs</th>
<th>Increases dispersion</th>
<th>Torsade de pointes in humans</th>
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<tr>
<td>Quinidine</td>
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<td>+</td>
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<tr>
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<tr>
<td>Ranolazine</td>
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*All these drugs prolong the action-potential duration and the QT interval (updated from Belardinelli et al. 2003). Data are from studies in canine LV wedge preparations.*

References