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Editors' view

Drug-induced long QT syndrome and drug development

J. M. Ritter, Editor-in-Chief British Journal of Clinical Pharmacology

Department of Clinical Pharmacology, School of Medicine at Guy's, King's College & St Thomas' Hospitals, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH UK

Introduction

September's issue is themed around cardiovascular clinical pharmacology. It includes articles on a range of topics, spanning a review of the role of the renin-angiotensin system in atrial fibrillation [1], through the effect of atorvastatin on high-sensitivity CRP in acute coronary syndrome [2], and the pharmacokinetics and pharmacodynamics of nicorandil in healthy and acute heart failure subjects [3] to the influence of paraoxonase-1 (PON-1) phenotype on the response of paraoxonase activity to statins [4]. Several papers [5–7] relate directly or indirectly to effects of drugs on the electrocardiographic QT interval, and it is on this subject that this Editors' View is focused.

The vulnerable period and the long QT syndrome

George Ralph Mines identified the 'vulnerable period' within the cycle of the cardiac action potential/pacemaker (or resting) potential [8]. (Mines [9], a contemporary at Cambridge of AV Hill, also described cardiac re-entry and identified the active principle of munchi arrow poison as strophanthin. He was appointed professor of physiology at McGill University in Canada aged 28, but died tragically soon thereafter – of which more later).

A ventricular extra beat falling early in the cardiac cycle, so that it coincides with ventricular repolarisation (the 'R on T' phenomenon), can provoke ventricular tachycardia (VT), and/or ventricular fibrillation (VF). The QT interval is measured from the beginning of the QRS complex (whether Q or R wave) to the end of the T wave. The latter may be difficult to define, especially when a U wave succeeds the T; however, the U wave tends to be isoelectric in lead aVL, which may be used to minimise this problem. Computerised algorithms greatly improve accuracy. The QT interval is influenced by heart rate, and corrections for this (such as Bazett's or Fridericia's: QTcB or QTcF) have been proposed.

Drugs and other conditions (including myocardial disease, stroke or head injury, hypocalcaemia and hereditary long QT syndromes) are associated with prolonged QTc, and can predispose to sudden death, especially in the setting of sympathetic nervous system activation. Welsh and Hoshi quote the case of a young woman who began to have black-outs aged three. These decreased in frequency as she got older. An ECG showed a prolonged QT interval. When 18 she lost consciousness running for a bus and when 19 she became quite emotional while participating in a live TV show and died [10].

Why is repolarisation a vulnerable period in the electrophysiological cycle of the heart?

The cardiac action potential is the product of interaction between voltage and various ligands with more than ten types of ion channel, so the situation is complex and made more so by the spatial inhomogeneities within the three dimensional network of the beating heart *in vivo*. Mutations in the sodium channel that influence sodium inactivation are implicated in the form of hereditary long QT syndrome mentioned above [10]. After-depolarisation (i.e. depolarisation after phase 0 of the cardiac action potential) is believed to be important. Early after-depolarisation occurs during ischaemia when a nonselective cation channel is activated by Ca^{2+}. Late after-depolarisation is also triggered by excessive Ca^{2+} entry. It results from activation of Na^{+}/Ca^{2+} exchange, which, because of its stoichiometry (it transports one Ca^{2+} ion out for three Na^{+} ions in), causes depolarisation. Both of these mechanisms are thus favoured by prolongation of the plateau of the action

potential, which is maintained in part by Ca^{2+} entry. Several of the Vaughan Williams classes of antidysrhythmic drugs prolong the action potential, especially class III antidysrhythmic drugs such as amiodarone and sotalol, but also some class I drugs (e.g. quinidine, flecainide), and it has long been known that these can cause arrhythmias as well as treat or prevent them. Indeed, this is thought to be the explanation for the adverse effects on mortality of D-sotalol and of flecainide in the SWORD and CAST studies respectively [11, 12], on which we commented in a recent Editors' View [13]. The particular dysrhythmia to which they predispose is a polymorphic form of VT in which the amplitude progressively waxes and wanes in a partly regular manner ('*torsade de pointes*') and which can degenerate into VF.

Drug-induced QT prolongation

It is now known that in addition to antidysrhythmic drugs many other therapeutic agents, including some tricyclic antidepressants, several antipsychotic drugs (e.g. thioridazine, droperidol, pimozide, olanzapine), antihistamines (e.g. terfenadine, astemizole), antimalarials (e.g. halofantrine), and quinolone antibiotics (e.g. moxifloxacin) also prolong QT, and several (but not all) of these drugs have also been linked to *torsade de pointes* and sudden death.

The extent of this problem is poorly understood. Molochia and her colleagues identified 40 surviving cases of drug-induced long QT syndrome (defined by the combination of *torsade de pointes*, QT prolongation and drug exposure) from 861 patients coded in hospital discharge summaries as arrhythmia or sudden cardiac death [5]. They estimate that the incidence of those that survive to reach hospital is 7.8–14.8 per million population per year. Importantly, their method of case ascertainment should enable future investigation of genetic susceptibility, which will be of great importance to regulators in the context of personalised medicine.

Mechanism of QT prolongation and drug regulatory requirements

The main mechanism of drug-induced QT prolongation is inhibition of the hERG* potassium channel [14], particularly in some patients with polymorphic variants of this ion channel [15]. This channel plays an important part in terminating the ventricular action potential via its contribution to the delayed rectifier potassium current. Structure – action relationship studies have identified chemical features associated with this effect, and some such entities are avoided at the early stages of drug design. Standard functional tests [16, 17] comprise:

- effect on hERG currents in cell lines expressing the hERG gene;
- measurements of action potential duration in myocytes from various parts of the heart in different species;
- measurements of QT intervals in conscious animals in which hERG-like channels cause ventricular repolarisation (ferrets or guinea-pigs rather than rats or mice, as well as larger mammals such as dogs, rabbits, or pigs, or in primates).

Alternative methods suitable for high-throughput screening, such as inhibition of binding of dofetilide (which has a high affinity for hERG channels), are widely used [17], but are not yet reliably predictive of lack of effect in the more time consuming functional tests mentioned above.

*for human ether-a-go-go-related gene – homologous to a Drosophila gene identified by a behavioural screen pioneered in the 1970s by Seymour Benzer.

Lamotrigine, QT interval, and safety

Furthermore, there is a danger of throwing the baby out with the bathwater. This is illustrated by an important negative study by Ruth Dixon and her colleagues in the current issue of the Journal [6]. Lamotrigine binds to hERG channels and inhibits the associated current, IKr with an IC_{50} of 229 $\mu mole.L^{-1}$. Could this be implicated in the increased risk of sudden unexplained death in people with epilepsy (estimated at 20–40 times the prevalence in the healthy population)? Dixon *et al.* addressed this in a careful PK-PD study in 153 healthy subjects. Moxifloxacin was used as a positive control, as recommended by ICH guidelines [16]. Both Bazett's and Fridericia's corrections were used and inspection of Figure 1 of their paper provides a rather convincing demonstration of the variation of uncorrected QT with RR interval (i.e. the inverse of heart rate) and of the tendency of Bazett's to overcorrect at short RR intervals and to undercorrect at long RR intervals, whereas the Fridericia-corrected QT does not vary obviously with RR interval. Steady-state exposure to doses of lamotrigine up to 200 mg twice daily caused small *reductions* in QTcF, so at these therapeutic doses *in vitro* inhibition of the delayed rectifier K^+ current does not translate into an effect on QT, presumably because the concentration at hERG channels is too low. Consistent with this, the median Cmax following the highest dose was approximately 37.5 $\mu mole.L^{-1}$, the expected unbound plasma concentration being approximately half this value. We should perhaps be grateful that lamotrigine – a valuable treatment for epilepsy and for bipolar disorder – was not nipped in the bud by current screening methods and never developed!

Cisapride

Cisapride, a gastric promotility agent that was withdrawn or restricted in most countries because of evidence of severe dysrhythmias, provides a different story. Despite structure – action, electrophysiological, and convincing case-report evidence, cardiac risk has not previously been confirmed in epidemiological studies. Sean Hennessy and his colleagues from the University of Pennsylvania argued that one potential explanation for this is that while two published epidemiological studies comprised approximately 9000 and 11 000 exposed person years respectively, they may still have been too small to detect an increase over the low baseline incidence of severe ventricular dysrhythmia (approximately 0.5–2 events per thousand person years) [7]. They identified 145 cases and 7250 controls in a larger nested case-control study. Cisapride was associated with a 2–3 fold increase in risk of hospitalisation for ventricular dysrhythmia and a nearly 8-fold increase in risk during the initial prescription period. Potentially dysrhythmogenic CYP3A4 inhibitors were themselves associated with increased risk, but there was no evidence of a pharmacokinetic interaction with cisapride. These results provide the first unequivocal epidemiological confirmation of an association between cisapride and serious dysrhythmia. This is important for a drug with therapeutic benefits that was particularly valued by paediatricians and neonatologists.

Concluding comments

A word of caution: while QT prolongation in functional studies appropriately flags the message 'proceed only with great caution', lack of such an effect (or even QTc shortening) does not imply that caution as to dysrhythmia can be thrown to the winds, since there are other important mechanisms that mediate cardiac dysrhythmias. Digoxin, which increases cytoplasmic Ca^{2+} indirectly by inhibiting the Na^+/K^+ pump and hence reducing cellular Ca^{2+} extrusion by reducing Na^+/Ca^{2+} exchange, is powerfully dysrhythmogenic at concentrations little greater than therapeutic. However, it actually *shortens* QTc, possibly by increasing vagal tone and hence IK_{ACh}. Which brings us back, via his work on the cardiac glycoside strophanthin, to George Ralph Mines whose tragic death aged 28 we mentioned above. Although unexplained (the autopsy showed that 'he appeared to be in excellent health [but] there were two incisions on his left arm and large amounts of fluid, as well as air in the arm' [18]), the circumstances of his death have some fascination for clinical pharmacologists. He was found unconscious in his laboratory by a janitor on a Saturday evening, connected to some physiological recording equipment [9]. Was he attempting some out-of-hours unaccompanied self-experimentation? We shall never know, although the fact that he discussed self-experimentation at the London Hospital on nerve injury by Henry Head and at Harvard on digestion by Cannon and Washburn during his inaugural address a month before his death is suggestive. Clinical pharmacologists of an independent frame of mind may reflect uneasily that perhaps those pesky and interfering modern day IRBs and oversight committees have their uses after all . . . With that somewhat unsettling thought, we wish our readers a very productive, exciting, but safe programme of human pharmacological investigation this autumn.

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