AN ANAESTHETIZED GUINEA PIG MODEL OF DRUG-INDUCED TORSADE DE POINTES

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Torsade de pointes (TdP) is a potentially lethal arrhythmia associated with long QT syndromes. It can be precipitated by altering cardiac repolarising currents, e.g. I_Kr and I_Ks with E-4031 and HMR1556 respectively. Previously, in anaesthetized animals given the α1-adrenoceptor agonist, phentylephrine, drug-induced TdP occurred in rabbits but not guinea pigs (Michael et al., 2006). I_Ks is larger in guinea pigs than in rabbits (Lu et al., 2001) and it has been suggested that β-adrenoceptor stimulation is essential for I_Ks to contribute to repolarisation (Volders et al., 2003). The aim of the present work was to investigate whether adrenaline, with both α- and β-adrenoceptor stimulatory effects, is required to reveal the torsadogenic action of I_K blockers in guinea pigs.

Experiments were performed in pentobarbital-anaesthetized, open-chest, male Dunkin-Hartley guinea pigs (340 to 490 g). They received three consecutive i.v. infusions of either vehicle (saline and polyethylene glycol-400, n = 4), E-4031 (3, 10 and 30 nmol kg\(^{-1}\) min\(^{-1}\), n = 8), HMR1556 (75, 250 and 750 nmol kg\(^{-1}\) min\(^{-1}\), n = 8) or E-4031 and HMR1556 combined (doses as above, n = 8). With each of the doses of I_K blockers they were also given rising doses of adrenaline (30, 60, 90, and 120 nmol kg\(^{-1}\) min\(^{-1}\)). QT intervals were measured along with short-term variability (STV) and triangulation of monophasic action potentials. Fisher’s exact test was used to compare arrhythmia incidences.

TdP (a polymorphic ventricular tachycardia with characteristic twists of the QRS complex visible on the electrocardiogram) occurred in 75%* of guinea pigs receiving the combination, but not in guinea pigs treated with the drugs alone or the vehicle (*P<0.05 combination vs. other treatments). Ventricular premature beats and ventricular tachycardia were observed in most guinea pigs. In contrast to the incidence of TdP, conduction disturbances were observed in 0%, 50%, 13% and 88% of guinea pigs given the vehicle, E-4031 alone, HMR1556 alone, and the combination respectively. However, there were no differences in the duration of conduction block among the treatment groups. The occurrence of TdP was not related to differences in the rate-corrected QT interval among the treatment groups. STV and triangulation were measured at baseline, before the first arrhythmia and before TdP. The STV values were 6.1 ±2.0, 6.8 ±2.3 and 4.8 ±1.0 ms respectively in guinea pigs that had TdP and 6.5 ±0.9, 8.2 ±1.4 and 5.2 ±0.6 ms at similar time points in those that did not have TdP. Triangulation values were 66 ±15, 63 ±7 and 51 ±11 ms (TdP-present) and 47 ±5, 46 ±5 and 44 ±4 ms (TdP-absent).

This is the first study to show that TdP can be induced by drugs in anaesthetized guinea pigs. Concomitant infusion of adrenaline was required to reveal the torsadogenic activity of combined administration of high doses of I_Kr and I_Ks blockers in vivo. The present findings also indicate that TdP could not be predicted by changes in QT intervals, STV or action potential triangulation.


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