

## THE EFFECTS OF ADRENERGIC AND CHOLINERGIC DRUGS ON DOFETILIDE-INDUCED ARRHYTHMIAS IN CONSCIOUS RABBITS

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The mechanisms of arrhythmias associated with acquired long QT syndrome are not fully understood. We tested the effects of anaesthesia as well as adrenergic and cholinergic drugs on QTc prolongation and proarrhythmic effects of dofetilide in conscious rabbits. Dofetilide was infused over 5 min at 20 min intervals (5, 10, 35, 100 and 350 µg/kg, i.v.) after a 60-min control period (n=9-11/group). Dofetilide prolonged the QTc interval (Bazett) in a dose-dependent manner with a peak effect of 38±4 %, which was fully abolished following chloralose-urethane anaesthesia. Phenylephrine (Phe) at low or high dose rates (2 and 8 µg/kg/min, i.v.) induced small (5.1±1.2%) and large (25.9±2.3%) increases in blood pressure and a consequent mild (-11.1±2.8%) and profound (-30.3±4.6%) bradycardia, respectively. Phe dose-dependently attenuated dofetilide-induced QTc lengthening. The low dose of Phe decreased but the high dose of Phe markedly increased the number of “torsade de pointes” (TdP) polymorphic ventricular tachycardia episodes (243 vs. 152 and 759, respectively, p<0.05). Atropine (40 µg/kg bolus and 20 µg/kg/h, i.v.) caused a small tachycardia, and decreased the number of TdP episodes (243 vs. 165, p<0.05). Isoproterenol (Iso, 1 µg/kg/min, i.v.) increased HR and diminished dofetilide-induced QTc prolongation, but metoprolol (Meto, 1 mg/kg bolus + 1 mg/kg/h, i.v.) slightly decreased HR. Iso induced small but Meto induced marked reductions in the number of TdP episodes. In conclusion, the dofetilide-induced QTc prolongation and proarrhythmic effects are modulated in a complex manner by agents affecting adrenergic or cholinergic receptors in the conscious rabbit.