The antiarrhythmic effects of a benzotriazinium salt in mice and guinea-pigs

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The benzotriazinium salt, 2-*n*-propyl-4-*p*-tolylamino-1,2,3-benzotriazinium iodide (TnPBI) has been reported to have effects on cardiac tissue which suggest that it may have potential use as an antiarrhythmic agent. These effects include class I and class III actions (Vaughan Williams, 1970) on guinea-pig atrial and ventricle cells (French & Scott, 1977) and antifibrillatory actions in guinea-pig Landendorff hearts (French & Scott, 1978). This paper describes the effects of TnPBI on halothane/adrenaline arrhythmias in the guinea-pig, and on aconitine-induced arrhythmias in the mouse.

Guinea-pigs were maintained under anaesthesia with 2% halothane in atmospheric air after induction with ether. Lead II ECG's were monitored on a Gould OS4000 storage oscilloscope. Adrenaline was then infused into a jugular vein at the rate of 12.5 $\mu g\ kg^{-1}\ min^{-1}$ by a motor driven syringe. This resulted in the appearance, within 2 min, of ventricular arrhythmias which persisted as long as the infusion continued. 5 min after the arrhythmias first appeared, four increasing doses of TnPBI (0.5, 1, 2 and 4 mg/kg) were injected into the other jugular vein at 3 min intervals. TnPBI converted the arrhythmias to sinus rhythm at all four dose levels, and a dose-related effect was observed in the duration of sinus rhythm induced. The lowest dose (0.5 mg/kg) caused reversion to sinus rhythm which persisted for approximately 7s, while the highest dose (4 mg/kg) maintained sinus rhythm for approximately 80 seconds.

Arrhythmias were induced in mice by a technique similar to that of Nwangwu, Holcslaw & Stohs (1977). Mice weighing between 20–25g were anaesthetised with pentobarbitone (75 mg/kg, i.p.), and Lead II ECG's were monitored as previously described. Arrhythmias were induced by infusing aconitine at 1.25 μg/min into a tail vein. In control animals this always resulted in arrhythmias progressing from ventricular bigeminy to ventricular tachycardia and finally to ventricular fibrillation and cardiac arrest. The antiarrhythmic effect was assessed as the increased amount of aconitine required to produce the first sign of arrhythmia (usually bigeminal rhythm) and to produce ventricular tachycardia, by comparison with untreated mice. Both events were usually abrupt in onset as the infusion progressed.

The antiarrhythmic activity of TnPBI was estimated from both chronically and acutely dosed animals. Chronically dosed mice were treated with TnPBI (5, 10 or 20 mg/kg) daily by i.p. injection for 20 days prior to aconitine challenge. Acutely treated mice received one of the above doses i.v. 3 min before aconitine challenge. All chronically dosed mice required significantly more aconitine per gram body weight to produce both bigeminal rhythm and ventricular tachycardia than untreated controls. Acute dosing with 5 mg/kg and 10 mg/kg also protected the mice against the two levels of arrhythmia: however, no statistically significant protection was afforded by TnPBI (20 mg/kg) although the aconitine doses necessary to produce arrhythmias were increased.

The short duration of action of TnPBI against halothane/adrenaline arrhythmias in the guinea pig may be related to a short plasma half-life of the compound. It is known that TnPBI is quite lipid soluble (Cull & Scott, 1973), thus it may distribute rapidly into body fat, and reduce the effective plasma concentration. This possibility is currently being investigated.

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References

CULL, G.A.G. & SCOTT, N.C. (1973). Structure-activity relationships in some series of 2-alkyl-1,2,3-benzotriazinium compounds. *Br. J. Pharmac.*, **47**, 819–826.

FRENCH, A.M. & SCOTT, N.C. (1977). A benzotriazinium salt as a potential antiarrhythmic agent. *Br. J. Pharmac.*, **61**, 131–132 P.

FRENCH, A.M. & SCOTT, N.C. (1978). The effects of a benzotriazinium salt on ventricular fibrillation in the guinea-pig perfused isolated heart. *Br. J. Pharmac.* (in the press).

NWANGWU, P.U., HOLCSLAW, T.L. & STOHS, S.J. (1977). A rapid *in vivo* technique for preliminary screening of antiarrhythmic agents in mice. *Arch. int. Pharmacodyn.*, **229**, 219–226.

VAUGHAN WILLIAMS, E.M. (1970). The classification of antiarrhythmic drugs. *In Symposium on Cardiac Arrhythmias.* ed Sandøe, E., Flenstedt-Jensen, E. and Olesen, K.H. AB Astra, Södertaljë, Sweden.