A method of producing permanent, complete atrioventricular block in the rat

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The production of permanent complete atrioventricular (AV) block has in the past meant open heart surgery (Bailey & Likoff, 1955) or thoracotomy (Hurwitz, 1971) or ingenious instrumentation (Babotai & Brownlee, 1971), none of which are readily compatible with small animal work. A simple and effective technique that has been used in the rat will be demonstrated.

Following induction of anaesthesia of the animal, the right jugular vein is exposed, and a length of 19 gauge stainless steel wire inserted through a cut in the wall. This probe is insulated along its length but exposed at its tip and is connected by the other end to the chest lead of the standard e.c.g. leads. Lead V is recorded as the probe is gently manipulated toward the right atrium by means of the length projecting from the vessel. Inspection of the lead V recording enables the experimenter to position the probe on the AV node. When properly located, mechanical AV block ensues, which is made permanent by connecting the probe to an Endofrex diathermy apparatus and ablating the node by the high current produced.

The probe is then withdrawn, complete (permanent) AV block verified using lead II e.c.g., the jugular vein either catheterized or tied off, and the animal allowed to recover.

No regression of the block has yet been encountered.

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Reversal of competitive neuromuscular blockade by RX 67668 in normal volunteers

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RX 67668 (cis-2-phenyl-1-(N-pyrrolidinyl) cyclohexane hydrochloride) is a potent anticholinesterase which is unrelated chemically to established cholinesterase inhibitors. It appeared from animal experiments (Doxey, Metcalf, Smith & Whittle, 1972) to have a greater affinity for nicotinic receptors at the neuromuscular junction than for muscarinic parasympathetic receptors. Its potential as an anticholinesterase in man has been assessed in four healthy young volunteers by comparing its ability to reverse partial competitive neuromuscular blockade with that of an established drug, neostigmine.

Twitches of the anterior compartment muscles of the leg were evoked by supramaximal stimulation of the lateral popliteal nerve at a frequency of 0·16 Hz using

a square wave stimulus of 1 ms duration applied through silver button skin electrodes. The twitches were recorded isometrically with a strain gauge and displayed on moving paper. When a steady baseline had been achieved D-tubocurarine was slowly injected over 5–15 min until the twitch amplitude had been reduced to approximately 50% of the control level. The total dose varied between 6 and 13 mg, but this was never sufficient to impair breathing. Three minutes later neostigmine (2·5 mg, preceded by 1·2 mg of atropine), RX 67668 (0·4 or 0·6 mg/kg) or an equivalent volume of saline was injected and the rate of recovery followed. Each subject received the three treatments on separate occasions, and was unaware of which treatment he had received.

Full recovery from the curare block was achieved in an average of 16 min after the injection of neostigmine. At the same point in time following the saline and RX 67668 (0·4 mg/kg) injections the recoveries were to 72% and 84% of the control values respectively (mean values of 2 subjects). The higher dose of RX 67668 produced no greater reversal than the low dose (85%, mean of 2 subjects).

Few adverse effects were seen with the low dose, but 0·6 mg/kg of RX 67668 produced nausea and distortions of body image. In a concomitant study, doses of up to 1 mg/kg were given to 5 healthy volunteers. These doses caused more severe adverse effects, including vomiting, dizziness and profuse sweating, in addition to the above effects. Muscarinic effects began to appear at doses above 0·6 mg/kg, but were slight.

It is concluded that RX 67668 produces marked central adverse effects in doses which have a weaker anticholinesterase effect than neostigmine at the human neuromuscular junction. It would therefore be unsuitable for clinical use.

REFERENCE

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