The actions of bretylium: adrenergic neurone blocking and other effects

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Commentary by

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Every young pharmacologist should read Sir Henry Dale's, 'Adventures in physiology with excursions into autopharmacology', (Dale 1953). This book contains selected reprints of Sir Henry's publications, describing some of the most important pharmacological discoveries made early this century. Each is usually preceded by comments by the author, outlining the circumstances leading to each finding. He emphasises how often chance observations, prompted his investigations. So it was with the discovery of bretylium and the class of drugs which later became known as the adrenergic neurone blocking agents.

Serendipity together with astute observation led Dale to make a wealth of discoveries in autonomic pharmacology, knowledge on which the discovery by F.F. Copp, A.F. Green and myself of bretylium (Boura *et al.*, 1959), the first clinically-used adrenergic neurone blocking agent, was based. Dale's investigations of the constituents of ergot identified one causing intense bradycardia after injection into anaesthetised cats, which he later identified as acetylcholine. He thus decided to examine the pharmacological properties of a series of esters and ethers of choline (Dale 1914). Their chemical structures reveal how close Dale must have been to finding the first adrenergic neurone blocking agent. However his interests were diverted by other major discoveries, leaving others to build on his work some forty years later.

Further investigation of the properties of ethers of choline, synthesised by Dr Peter Hey, was undertaken by Professor W.A. Bain and colleagues at Leeds University, during the 1950s. Both Hey and the pharmacologists involved were particularly interested in the relationships between the chemical structures of these agents and their nicotinic agonist properties. More serendipity, interacting with minds of trained investigators, led to an exciting observation. Unexpectedly one compound, choline 2,6-xylylether bromide (xylocholine, TM 10), inhibited contractions of the nictitating membrane of the anaesthetised cat in response to electrical stimulation of the superior cervical sympathetic nerve. They showed that this action could not be due to either antagonism of the adrenergic transmitter or ganglion blockade. Parasympathomimetic effects were additionally noticed. These precluded clinical use of xylocholine for inhibiting peripheral sympathetic nerve function, thus lowering arterial blood pressure, as a treatment for hypertension. I found later that the parasympathomimesis was extremely prominent. Unanaesthetised cats responded to subcutaneous xylocholine not only by narrowing of the palpebral fissures, relaxation of the nicitating membranes and miosis indicative of reduced sympathetic tone, but also by long lasting profuse, lachrymation, salivation, vomiting and diarrhoea. Nevertheless one of the Leeds group, Dr Roy Fielden, agreed to receive it (Fielden 1981). His decision emphasises, in addition to heroism, the need at that time for improved antihypertensive drugs. Introduction of hexamethonium (Paton & Zaimis 1952), and other ganglion blocking agents into clinical medicine had demonstrated that reducing arterial blood pressure, by blockade of transmission in sympathetic ganglia, prolonged life of hypertensive patients. However side effects that frequently adversely affected the quality of life were an inevitable consequence of the unavoidable concomitant blockade of transmission in parasympathetic ganglia.

The acute properties of xylocholine were described by the Leeds workers, to a meeting of The British Pharmacological Society in 1956. With hindsight, it is strange that of the numerous industrial pharmacologists attending, only one

apparently appreciated the full implication of the Leeds group's findings; that they had established a possible lead towards developing novel hypotensive agents free from the side effects of ganglion blockade. This was A.F. Green, who led a small team of pharmacologists, at The Wellcome Research Laboratories, Beckenham. It was my good fortune to join Wellcome at that time, after an excellent training in pharmacology as H.O. Schild's technician for eight years and as an undergraduate, at University College, London. So Green suggested that I should undertake the laboratory experimentation.

Detailed descriptions of the work that lead to the discovery of bretylium and to an understanding of its mode of action have been given in a number of reviews (for references see Fielden, 1981; Boura & Green, 1984). Green and I decided that the first need was to find a xylocholine-like compound having its ability to inhibit sympathetic nerve function, but without parasympathomimetic properties. Secondly it was of obvious importance to establish the total pharmacology, including mode of action, of any new compound of interest.

Xylocholine is a quaternary ammonium compound. We therefore looked for a drug possessing its specific sympathetic blocking ability, amongst quaternary ammonium salts, previously synthesised at Wellcome. A large number were available for study, dictating the necessity for early establishment of methods that rapidly eliminated those with unwanted activities. Not surprisingly, for compounds structurally related to acetylcholine, many were found to cause effects mediated by acetylcholine receptors. Nicotinic, muscarinic and neuromuscular blocking properties were common.

Weak peripheral sympathetic nerve blocking properties were first identified in the quaternary ammonium compound bephenium. This agent, synthesised by Dr F.C. Copp as an anthelmintic, had no other overt xylocholine-like actions. Consequently it was the starting point for synthesis by Copp of a large number of quaternary ammonium salts. As time went on our knowledge gradually increased of the relationship between the structures of these agents and their wanted and unwanted activities. One, BW 25c57 (the 25th synthesised during 1957), powerfully blocked sympathetic postganglionic nerves. Following its subcutaneous administration to unanaesthetised cats a slowly developing relaxation of the nictitating membranes and miosis occurred. A puzzling aspect of these effects was that the delay in onset of the membrane relaxation became longer as the dose was increased, not shorter as was expected. Further examination of the drug showed that it caused pronounced sympathomimetic effects, after intravenous administration to anaesthetised cats, manifested by nictitating membrane contraction, a pressor effect and tachycardia. The magnitude of the contraction of the nictitating membrane was proportional to dose and obviously sufficient to initially offset membrane relaxation caused by the concomitant blockade.

Many other members of the series were also found to have sympathomimetic properties. Eventually, after examination of its ortho fluoro, chloro and iodo analogues, BW 373c57 (N-o-bromobenzyl-N-ethyl-NN-dimethyl ammonium bromide) was chosen for detailed examination. It possessed minimal sympathomimetic and parasympathomimetic properties, had sufficient potency and also a relatively long lasting duration of action in cats. The compound was given the open name bretylium, approved by the British Pharmacopoeia Commission, after a suggestion by Copp who derived it from the chemical name. Later its tosylate salt was developed, since bromism in man was possible if the bromide was taken repeatedly.

Further work demonstrated that bretylium specifically depressed noradrenergic neurone function, sympathetic pre- and postganglionic cholinergic neurones being little affected. We also found that all peripheral sympathetic postganglionic nerves examined were blocked, although some were more susceptible to the drug than others. Unlike ganglion-blocking drugs, release of catecholamines from the adrenals was not depressed. That the depression of noradrenergic nerves was due to inhibiton of noradrenaline release at the terminal synapse was relatively easy to determine. However, establishing how the drug dissociated the postganglionic nerve impulse from its ability to release transmitter was much more difficult. A number of ingenious theories was put forward, each with its various advocates. We thought a local anaesthetic-like effect as the nerve terminals most likely, after finding that bretylium caused long lasting local anaesthesia and that high concentrations accumulated in noradrenergic neurones. This intraneuronal uptake was later found to be due to the neuronal amine pump. Eventually Brock and Cunnane (1988), after electrophysiological techniques had improved, produced data

supporting our original hypothesis. They showed that bretylium did cause a local anaesthetic-like effect at noradrenergic nerve terminals.

One thing that worried Copp, when he first saw the effects of his drug on the arterial blood pressure of supine anaesthetised cats, was that there was no convincing hypotension. On the contrary its mild sympathomimetic properties often maintained arterial blood pressure, at a time when a number of parameters indicated that maximal adrenergic neurone blockade had developed. We mentioned that man was a vertical animal and postural hypotension a likely consequence of adrenergic neurone blockade in patients, and to make sure injected bretylium into a vertically positioned anaesthetised cat. A very convincing depressor response followed a small intravenous dose. The drug's ability to cause this effect was re-emphasised when the first volunteer Dr R. Moulton, in The Medical Unit, University College Hospital received bretylium. After intravenous injection in the supine position, of what turned out to be rather a large dose, he sat up and his blood pressure became unrecordable by auscultation. Postural hypotension persisted for eight hours (Boura *et al.*, 1959).

Early on we noticed that tolerance rapidly developed to the inhibitory actions of bretylium in animals, particularly after repeated administration of large doses. This was reported in our first clinical publication, but at that time had not been found to be a problem during use of lower doses in man (Boura *et al.* 1959). However, as bretylium's clinical use expanded, it was realised that onset of tolerance to its hypotensive effect was rapid and unacceptable.

Ideas, regarding possible mechanisms underlying tolerance to bretylium, stimulated much debate between Green and myself. After a stimulating exchange of views, over the 'phone one weekend, I tested our latest idea the following week, using cats that had received daily injections of bretylium for some months. Our reward was evidence supporting the new hypothesis. Tolerance was due to development by terminal effector tissues of postganglionic denervation supersensitivity to the transmitter. During low frequencies of nerve stimulation, this was sufficiently great to offset the reduced noradrenaline output caused by the drug. There is relatively little depression of transmitter release by bretylium during low rates of nerve traffic. Higher rates are affected to the greatest extent. Thus we obtained the knowledge necesary to find bethanidine, a successor superior to bretylium in a number of respects. Today, thirty five years after those exciting times, bretylium remains in clinical use for treatment and prophylaxis of ventricular fibrillation.

Acknowledgments

It is a pleasure to acknowledge the essential roles of the late Dr Alan Green, and my friend and former colleague Dr Fred Copp who synthesised bretylium and other adrenergic neurone blocking agents. Unfortunately space constraints have not allowed credit to the many other collaborating workers recognised in our publications.

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