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DEPRESSION OF THE VASOMOTOR CENTRE BY MECAMYLAMINE, INDEPENDENT OF ITS GANGLION-BLOCKING ACTIVITY

BY

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Mecamylamine depressed the vasomotor centre independently of its ganglion-blocking action. The central action was elicited by small amounts of the drug when it was confined to the central nervous system of dogs and cats anaesthetized with pentobarbital sodium and of spinal cats. The spinal site of action was shown by the inhibition of vasomotor responses due to spinal compression in cats, when mecamylamine was introduced intrathecally in a dose too small to block autonomic ganglia. The supraspinal site of action was shown by intravertebral arterial injection of mecamylamine into cats, which caused hypotension and selectively blocked the electrically evoked pressor responses from the medulla without affecting the "nicotinic" ganglionic responses to acetylcholine. Injection of mecamylamine into the cerebral ventricles of dogs produced hypotension, and the reflex vasomotor responses to stimulation of afferent fibres in the vagus nerves and to occlusion of the common carotid arteries were inhibited without any change in the response of the nictitating membrane to preganglionic nervous stimulation.

Mecamylamine, a secondary amine, is an orally effective ganglion-blocking agent (Stone, Torchiana, Navaroo & Beyer, 1956); it readily penetrates the "blood-brain barrier" (Bennett, Tyler & Zaimis, 1957). Several clinical reports (Doyle, Murphy & Neilson, 1956; Doyle & Neilson, 1956; Schneckloth, Corcoran, Dustan & Page, 1956; Smirk & McQueen, 1957; Perry & Schroeder, 1957) mention side effects such as muscular weakness, choreiform movements, sensations of nervousness and anxiety, acute mania and convulsive seizures which are probably due to an action of mecamylamine on the central nervous system. Studies in rats (Corne & Edge, 1958; Spinks, Young, Farrington & Dunlop, 1958) also indicate a central action of the drug.

The hypotensive action of mecamylamine is commonly attributed to its potent ganglion-blocking property. However, Rubinstein, Pedersen, Fakstorp & Ronnov-Jessen (1958) suggested a predominantly central hypotensive action of the drug from the observation that the hypotension induced by mecamylamine persisted and that the carotid arterial occlusion reflex remained suppressed even after the contractions of the nictitating membrane due to preganglionic nerve stimulation had returned to normal. McCubbin & Page (1958), using electroneuronographic techniques, and Murray, Beck, Rondell & Bohr (1957), using cross-circulation techniques, could not detect a central action of mecamylamine.

The purpose of the present study was to obtain more direct evidence of a central vasomotor depressant action of mecamylamine, independent of its ganglion-blocking action. To overcome masking of the central action by the peripheral ganglionic-block the drug was introduced into the lateral cerebral ventricle or into the spinal theca, or it was injected into a vertebral artery, or intravenously in a dose too small to produce ganglionic-block.

METHODS

Dogs and cats were anaesthetized with pentobarbital sodium (30 mg/kg intravenously into dogs, and 35 mg/kg intraperitoneally into cats), bilaterally vagotomized and maintained on artificial ventilation. Blood pressure was recorded from the left common carotid artery by means of a mercury manometer writing on a kymograph. Intravenous injections were made through an indwelling polyethylene tube introduced into a femoral vein. Injections into the cerebral ventricles of the dog were made through a polyethylene cannula following the technique of Bhargava & Tangri (1959). Intrathecal injections into the cat were made through a hypodermic needle introduced at the lumbosacral articulation.

The action of mecamylamine on central vasomotor areas was assessed by observing the effects of the drug on (*a*) the reflex pressor responses to occlusion of the right common carotid artery and to electrical stimulation (rectangular waves) of the central cut end of the right vagus nerve, and on (*b*) the pressor responses to direct electrical stimulation of the medullary vasomotor centre through a bipolar needle-electrode oriented by means of the Horsley-Clarke stereotaxic technique. The positioning of the electrode was aided by the parameters described by Wang & Ranson (1939). The action of mecamylamine on the spinal cord was studied by observing the vasomotor responses to spinal compression by the technique of Bhargava & Kulsreshtha (1959).

The responses employed to detect the ganglion-blocking action of mecamylamine were (i) the contractions of the nictitating membrane elicited by stimulation of the preganglionic cervical sympathetic nerve, and (ii) the pressor (" nicotinic ") responses following injection of acetylcholine after administration of atropine.

RESULTS

Studies in cats

Effect of mecamylamine on the spinal vasomotor areas. The effect of mecamylamine on the vasomotor response to spinal compression was studied in ten cats. On intravenous administration, the minimum dose of mecamylamine which produced a detectable ganglionic-block was 0.3 mg/kg, but with this dose the vasomotor response to spinal compression was also blocked. Smaller doses blocked neither ganglia nor the response to compression.

Mecamylamine was therefore given intrathecally in a dose inadequate to block ganglia and its effect on the vasomotor responses to spinal compression was studied. Fig. 1 shows the effects of intrathecal injection of mecamylamine in a total dose of 0.1 mg into a cat of 2.5 kg. After 20 min, the vasomotor response to spinal compression was inhibited and the resting blood pressure level fell by 20 mm Hg. Complete recovery of the response occurred at 90 min. Thus, mecamylamine inhibited the spinal vasomotor areas when introduced directly into the spinal theca, in a dose which could not have produced ganglionic-block even if peripheral leakage had occurred.

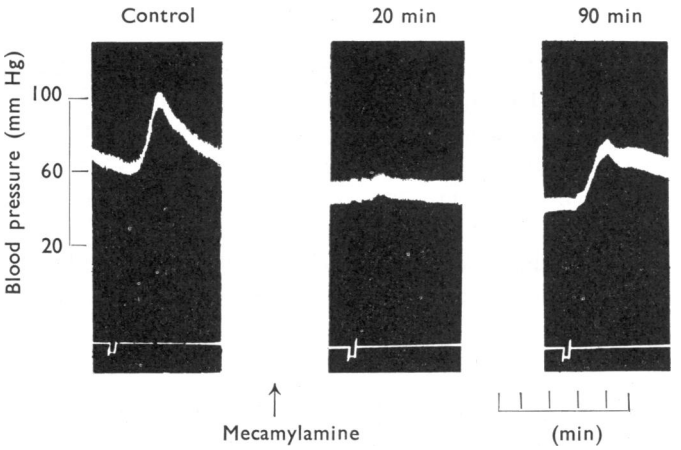

Fig. 1. Effect of intrathecal administration into a spinal cat (2.5 kg) of mecamylamine (0.1 mg) on the vasomotor response to spinal compression with a pressure of 150 mm Hg for a period of 10 sec. The response was blocked 20 min after intrathecal administration of mecamylamine. Almost complete recovery had occurred in 90 min.

Effect of mecamylamine on the medullary vasomotor areas. To localize the mecamylamine to the brain the drug was injected into a vertebral artery (in three experiments) in a dose which was about one-tenth of that necessary to block peripheral ganglia when given intravenously, and pressor responses were evoked by electrical stimulation of the medulla oblongata. Results of one such study are shown in Fig. 2. After 10 min from the injection of mecamylamine (0.03 mg/kg) the pressor response to medullary stimulation was completely inhibited and the resting blood pressure level was lowered by 30 mm Hg. Recovery of the pressor response occurred after 120 min. The response to preganglionic stimulation was unaffected. This experiment clearly demonstrates the depression of the vasomotor centre by mecamylamine, independent of any ganglion-blocking action.

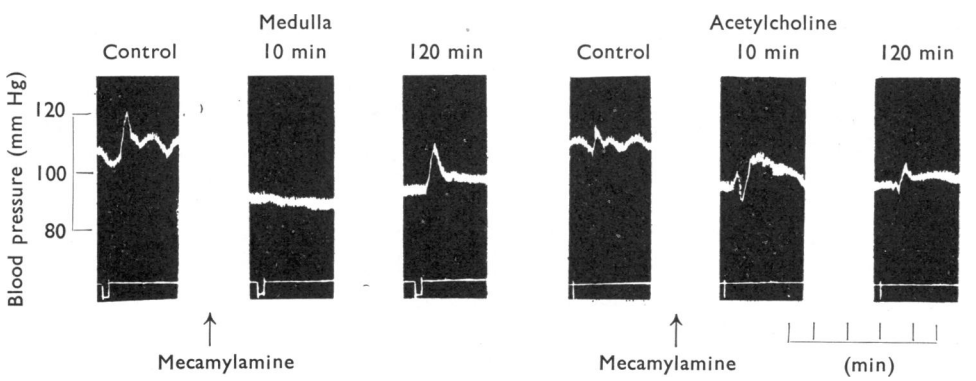

Fig. 2. Effects of mecamylamine (0.03 mg/kg injected into the left vertebral artery) on the pressor responses evoked by electrical stimulation (rectangular pulses, 2.0 V, 60 shocks/sec) of the medulla using stereotaxic technique (left-hand records), and on the simultaneous "nicotinic" response to acetylcholine (right-hand records). Note the selective block of the medullary response at 10 min, with recovery in 120 min.

Studies in dogs

Effect of mecamylamine on cardiovascular reflexes. Mecamylamine was injected into the lateral cerebral ventricles of eight dogs to gain direct access of the drug to the central nervous vasomotor areas. The results of one such study are shown in Fig. 3. Mecamylamine (3.0 mg total) was injected into a lateral cerebral ventricle. After 30 min the blood pressure had fallen by 20 mm Hg, whilst the vasomotor response to stimulation of the central end of the cut vagus and the pressor response to carotid arterial occlusion were considerably reduced. Complete recovery of the reflex vasomotor response occurred after 90 min. The response of the nictitating

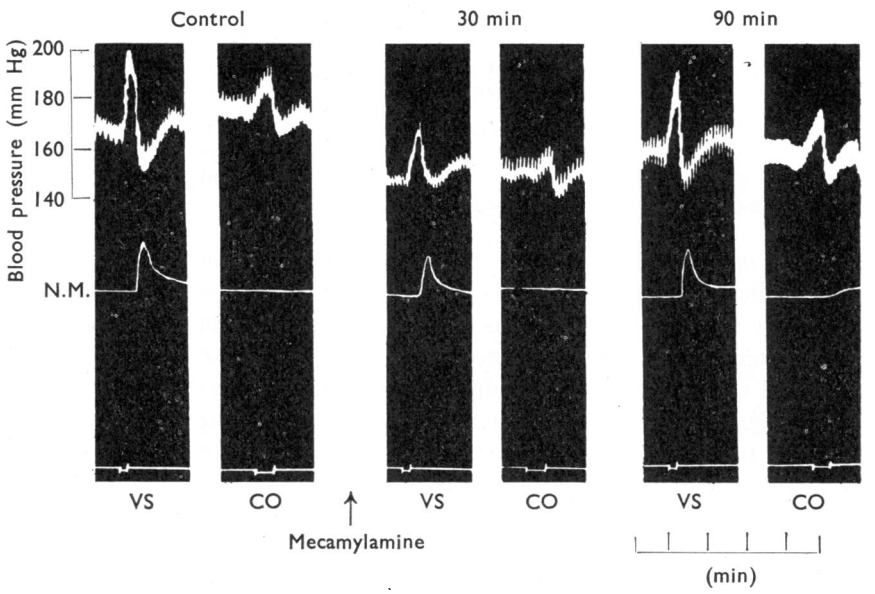

Fig. 3. Effects of mecamylamine (3.0 mg administered into a lateral cerebral ventricle of a dog) on reflex vasomotor responses to electrical stimulation (10.0 V, 10 shocks/sec for 10 sec) of the central cut end of a vagus nerve (VS) and to occlusion of a common carotid artery (CO). Tracings from above down: blood pressure, contractions of a nictitating membrane (N.M.) and signal. First two panels: control. At 30 min after injection of mecamylamine, the blood pressure had fallen and both the reflex vasomotor responses were depressed, but there was little change in the response of the nictitating membrane. Recovery occurred in 90 min.

membrane to preganglionic stimulation remained almost unaltered throughout the experiment. This experiment demonstrated the direct depression of the reflex vasomotor responses by injection of mecamylamine into the cerebral ventricles, independent of any ganglion-blocking action.

DISCUSSION

When ganglion-blocking agents are administered parenterally it is difficult to detect any action on the vasomotor centre unless an effectve dose can be found which does not block autonomic ganglia. With pempidine the central vasomotor

action was seen with an intravenous dose too small to produce ganglionic-block (Dhawan & Bhargava, 1960). However, with mecamylamine such a dose could not be found.

The central vasomotor effects of peripherally acting drugs have been studied (i) electroneuronographically (Dontas & Nickerson, 1957 ; McCubbin & Page, 1958), (ii) by cross-circulation experiments (Murray *et al.*, 1957) and (iii) by injections into the cerebral ventricles, the vertebral arteries or intrathecally.

Electroneuronographic techniques have yielded divergent results when the same drug was studied by different groups of investigators. The discrepancies may be due to reflex alterations in the splanchnic efferent nerve potentials resulting from changes in the blood pressure. Thus when used by itself the electroneuronographic technique cannot be relied upon to detect any central vasomotor activity of a drug with potent peripheral ganglion-blocking actions.

Cross-circulation experiments may involve extensive trauma. Hypotension in the head of the recipient animal may result from block of the superior cervical ganglion, and ischaemia of the vasoactive neurones may occur due to shunting of blood from intra- to extra-cranial structures. It is therefore necessary in such studies regularly to assess the reactivity of the vasomotor centres. Unfortunately, Murray *et al.* (1957) did not describe any test of viability of the vasomotor neurones and the lack of central effect of ganglion-blocking agents in their study may have been due to lack of vasomotor centre reactivity.

In the present investigation mecamylamine was injected into the cerebral ventricles and into the vertebral arteries to gain a direct access of the drug to the vasomotor areas in the spinal cord and medulla and to obviate any ganglion-blocking action of the drug. In all these experiments the ganglionic responses either to electrical stimulation or to acetylcholine were recorded before and after the administration of mecamylamine to detect simultaneously any ganglionic action of the drug. In the experiments where mecamylamine was injected into the spinal theca a control response to detect any ganglionic-block was unnecessary since the amount of drug injected was too small to produce any effect on the autonomic ganglia.

Localization of the drug in the central nervous system (by injection into a cerebral ventricle or a vertebral artery) inhibited the reflexly and directly evoked vasomotor responses without altering the ganglionic response. An inhibitory action of mecamylamine at the spinal level was also demonstrable when the drug was given intrathecally.

The relative importance of central nervous and ganglionic-block in the hypotensive response to mecamylamine cannot be stated precisely. In the experiments of Stone *et al.* (1956) as well as in the present study, the fall of blood pressure after intravenous injections of mecamylamine preceded ganglionic-block. It may be that in the initial stages of the effect of mecamylamine the central component of action is predominant whilst the prolonged hypotensive response is the result of ganglionic-block.

A preliminary report of this work was presented to the Annual Conference of the Association of Physiologists and Pharmacologists of India in 1960.

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