CENTRAL VASOMOTOR EFFECTS OF A NEW GANGLION-BLOCKING AGENT—1 : 2 : 2 : 6 : 6-PENTAMETHYL PIPERIDINE (PEMPIDINE)

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The central vasomotor effects of pempidine were studied in dogs and cats anaesthetized with pentobarbitone sodium, and in spinal cats. Pempidine lowered the threshold of electrical stimulation of the medulla oblongata to evoke a pressor response when given intravenously to cats in a dose insufficient to block autonomic ganglia. Injection of a small dose into the cerebral ventricles of dogs produced an increase in the pressor responses to occlusion of the carotid artery and to electrical stimulation of the central end of the cut vagus. In the spinal cat small doses of pempidine, given either intravenously or intrathecally, augmented the rise in blood pressure resulting from compression of the spinal cord. Since all these effects were produced by pempidine in doses insufficient to cause ganglionic block, the observed effects are attributed to central facilitation of the vasomotor responses. Thus pempidine has a stimulant action on the spinal and supraspinal centres.

It is known that piperidine derivatives block ganglionic transmission; for example, Zamboni and Borghetti (1953) reported ganglion-blocking properties of N-ethyl piperidine. The pharmacology of 1:2:2:6:6-pentamethyl piperidine (pempidine) was independently reported by Spinks and Young (1958) and Corne and Edge (1958). This drug has a prolonged hypotensive effect attributed to strong and persistent ganglionic blockade. Harrington, Kincaid-Smith and Milne (1958) have shown that pempidine on parenteral administration passes through the blood-brain barrier and is then taken up by the brain. The present study was undertaken to determine possible central vasomotor effects of pempidine, independent of its ganglion-blocking action.

The main difficulty in the study of the central vasomotor effects of ganglion-blocking agents is that peripheral ganglionic blockade masks the central vasomotor effects of these agents (Dontas and Nickerson, 1956). To overcome this difficulty the drug was injected into the cerebral ventricles or intrathecally, or it was given intravenously in a dose too small to produce ganglionic blockade.

METHODS

The investigation was carried out in dogs and cats anaesthetized with pentobarbitone sodium (30 mg./kg.

intravenously in dogs, and 35 mg./kg. intraperitoneally in cats). The animals were maintained on artificial respiration after cutting both vagi. Blood pressure was recorded from the left carotid artery. The intravenous injections were made through a polythene tube into a femoral vein, the intraventricular injections were made into the lateral ventricle as described by Bhargava and Tangri (1959), and the intrathecal injections through a needle inserted in the vertebral canal at the lumbosacral articulation.

The action of the drug on the brain stem was assessed by observing the effects on (a) the reflex pressor response obtained by occlusion of the right carotid artery, and by electrical stimulation of the central cut end of the right vagus nerve (by means of an electronic stimulator), and (b) on the pressor responses evoked by direct electrical stimulation of the medulla oblongata by means of a bipolar needle electrode using a stereotaxic technique. The electrode placement was aided by the parameters described by Wang and Ranson (1939). The site of action of the drug in the spinal cord was assessed by observing the effects on the vasomotor responses elicited by the technique of spinal compression in the spinal cat (Bhargava and Kulsreshtha, 1959). Contractions of the nictitating membrane were obtained by pre-ganglionic stimulation of the cervical sympathetic nerve, and pressor ("nicotinic") responses by injection of acetylcholine after atropine.

Pempidine was used as the hydrochloride.

FIG. 1.—Records of arterial blood pressure (upper tracing) and of the nictitating membrane (lower tracing) of a dog, 7.2 kg., anaesthetized with pentobarbitone sodium. CO, response to 30 sec. occlusion of the carotid artery. CV, response to electrical stimulation (4 V, 10 msec., 10/sec. for 10 sec.) of cut end of the central stump of the vago-sympathetic nerve. (a) Control, (b) 10 min. after intraventricular injection of 50 μ g. of pempidine, (c) 15 min. after intravenous injection of 0.5 mg./kg. of pempidine. Time signal in 30 sec.

FIG. 2.—Record of arterial blood pressure of a cat, 3.0 kg., anaesthetized with pentobarbitone sodium. CO, response to 30 sec. occlusion of the carotid artery. 0.5 V, 1.0 V, 2.0 V; electrical stimulation of the medulla oblongata by means of a bipolar electrode using a stereotaxic technique. (a) Control, (b) 15 min. after intravenous injection of 25 μ g. pempidine. Time signal in min. Note potentiation of all the vasomotor responses.

FIG. 3.—Record of arterial blood pressure of a spinal cat, 3.0 kg. Upper tracing shows vasomotor responses to compression of the spinal cord (150 mm. Hg for 10 sec.). Lower tracing shows “nicotinic” pressor responses to 150 μ g. acetylcholine after atropine. Time signal in min. (a) Control, (b) 20 min. after intravenous injection of 25 μ g./kg. of pempidine, (c) 10 min. after intrathecal injection of 5 μ g./kg. of pempidine. Note the increased responses to spinal compression whereas those to acetylcholine were unaltered.

RESULTS

The Reflex Vasomotor Responses in the Dog After Injection of Pempidine into the Cerebral Ventricles

The effects of intraventricular administration of pempidine (50 to 100 μ g.) on reflex supraspinal vasomotor responses were studied in 3 dogs. The results of one experiment are shown in Fig. 1. The control records (CO) show the pressor responses to occlusion of the carotid artery for 30 sec. (CO), and the pressor response as well as the nictitating membrane contraction obtained by electrical stimulation of the central cut end of the vagosympathetic trunk (CV). On intraventricular

administration of 50 μ g. pempidine the blood pressure rose about 10 mm. Hg, and both the reflex vasomotor responses increased. The pressor response to occlusion of the carotid artery increased from 30 to 80 mm. Hg, and the response to central stimulation of the vagus increased from 30 to 45 mm. Hg. The contraction of the nictitating membrane was unchanged. The subsequent intravenous injection of 0.5 mg./kg. pempidine produced a marked fall of arterial blood pressure of 50 mm. Hg, and abolished both the reflex vasomotor responses (CO and CV). The nictitating membrane response was also abolished, therefore the inhibition of the vasomotor responses can be attributed solely to ganglionic blockade.

The Vasomotor Responses in the Cat After Intravenous Injection of Pempidine

The results were essentially the same in 3 cats. Fig. 2 illustrates the graded pressor responses evoked by electrical stimulation of the medulla with increasing voltage and the pressor response to the 30 sec. occlusion of the carotid artery (CO). Fifteen min. after the intravenous injection of pempidine (25 $\mu\text{g./kg.}$) all these vasomotor responses were increased. The control response to 1.0 V was now obtained with 0.5 V, and that to 2.0 V with 1.0 V. Thus the threshold of medullary excitability was lowered after the pempidine administration.

Spinal Vasomotor Responses After Pempidine in the Spinal Cat

The effect of pempidine on the spinal vasomotor responses was studied in 8 cats after intravenous injection of 25 to 50 $\mu\text{g./kg.}$ and in 3 of these also after intrathecal administration of 5 $\mu\text{g./kg.}$ Fig. 3 shows the vasomotor responses to spinal compression (upper record), and the "nicotinic" pressor responses to 150 $\mu\text{g.}$ of intravenous acetylcholine after atropine (lower record). After intravenous administration of pempidine (25 $\mu\text{g./kg.}$) the blood pressure rose 10 mm. Hg. Twenty min. later, the vasomotor response to spinal cord compression was increased. When 5 $\mu\text{g./kg.}$ of pempidine was given intrathecally after 1 hr. and the spinal cord was then compressed 10 min. later, the vasomotor response was further increased. This augmentation of the response persisted for 1.5 hr.

After intravenous injection of 25 $\mu\text{g./kg.}$ pempidine the augmented response to compression of the spinal cord appeared within 10 to 20 min. and persisted for 1.5 hr. In one cat in which 50 $\mu\text{g./kg.}$ was injected intravenously the blood pressure was lowered and the response to compression of the spinal cord was depressed within 10 min. and abolished within 30 min., but this also occurred with the response to acetylcholine. In this experiment this dose of pempidine must, therefore, already have exerted its effect on ganglionic transmission.

DISCUSSION

The results of the present investigation showed that pempidine has a central vasomotor stimulant effect at the supraspinal as well as at the spinal level. This central effect which was examined on reflex vasomotor responses is best seen when the drug is injected into the cerebral ventricles or intrathecally. On intravenous administration it can only be seen when the dose injected is too small to produce ganglion-block.

A pressor action of pempidine resulting from large intravenous doses has been reported by Corne and Edge (1958) in cats with a low blood pressure. The pressor action was not blocked by bilateral adrenalectomy or by administration of phenoxybenzamine. However, the observation that the pressor response was considerably reduced after spinal cord destruction suggests that the effect was at least partly a result of a central action. The observation that pempidine in doses insufficient to block the ganglia manifests a central vasomotor stimulation may have a bearing on its clinical use. Small doses of pempidine may raise the blood pressure by its central action, but with adequate dosage hypotension must be produced by its ganglion-blocking effect.

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