Brit. J. Pharmacol. (1957), **12**, 457.

THE EFFECTS OF MECAMYLAMINE IN THE CAT AS MODIFIED BY THE ADMINISTRATION OF CARBON DIOXIDE

BY

J. P. PAYNE AND G. G. ROWE

From the Department of Anaesthesia and Department of Medicine, Postgraduate Medical School of London

(RECEIVED MAY 17, 1957)

A series of cats, anaesthetized with chloralose, was given intravenously a sufficient quantity of mecamylamine to produce hypotension and a 50% neuromuscular block. Inhalation of carbon dioxide then produced a further depression of blood pressure and an increase in the neuromuscular blocking effect. It was shown that, following the administration of carbon dioxide, the plasma mecamylamine levels increased coincident with the increased pharmacological effects.

Since its introduction as a ganglion blocking agent, mecamylamine (3 methyl amino*iso*camphane hydrochloride) has been known to possess a weak blocking action at the neuromuscular junction (Stone, Torchiana, Navarro and Beyer, 1956). Relatively large doses of the drug are required before this action appears, and it is unlikely that, under normal circumstances, this property will present any clinical problems. Nevertheless, in the experimental animal the effects of mecamylamine at the motor end plate may help to throw light on its mode of action.

During the administration of mecamylamine there is evidence that considerable quantities are stored in the tissues whereas the plasma level remains low (Milne, Rowe, Somer, Meuhrcke, and Crawford, 1957). The present study indicates that when carbon dioxide is inhaled by a cat previously given mecamylamine, the plasma level of mecamylamine is raised, the neuromuscular block is potentiated and the hypotensive effect is intensified.

METHOD

Nine healthy but otherwise unselected cats were anaesthetized with chloralose (80 mg./kg.) after induction with ethyl chloride and ether. A tracheal cannula was inserted, and artificial respiration established by means of an "Ideal" respiration pump. This method was employed to avoid the risk of hypoxia during neuromuscular block and to facilitate the administration of carbon dioxide. Neuromuscular blocking activity was assessed using the nerve muscle preparation described by Brown (1938). In these experiments the tendon of the tibialis anterior muscle was isolated and connected to a flat spring myograph writing on a smoked drum. The lateral branch of the sciatic nerve was exposed in the thigh and shielded platinum electrodes applied to it. The stimulus was a rectangular pulse of 0.5 msec. duration applied at 10 sec. intervals and was maximal at a strength of 1 to 3 V. The blood pressure was measured from the common carotid artery with a mercury manometer. The intravenous injections were given into the right external jugular vein cannulated for the purpose.

The possibility of a direct depressant effect by mecamylamine on muscle was excluded by stimulating the tibialis anterior directly in one cat. When this occurred the muscle contracted normally even after mecamylamine had reduced the twitch by 50% on indirect stimulation.

Mecamylamine was given by a divided dose technique recommended by Paton (personal communication) so that the amount required to produce a standard degree of neuromuscular block could be more readily measured. An initial injection of 5 to 10 mg./kg. was given followed by equal increments until a 50% reduction in twitch size was obtained. This was taken as standard for these experiments and was attained with a total dose of 40 to 50 mg./kg. mecamylamine. When hypotensive and blocking activity had stabilized approximately 30 min. after the final mecamylamine injection, 10 or 20% (v/v), carbon dioxide was administered for periods of 10 to 30 min. Samples of blood and muscle and in some instances other tissues were taken immediately before and approximately 30 min. after mecamylamine administration, after the maximum effects of carbon dioxide and on recovery from these effects. The mecamylamine content of these samples was estimated by the method described by Baer, Paulson, Russo, and Beyer (1956) modified from Brodie, Udenfriend, Dill,

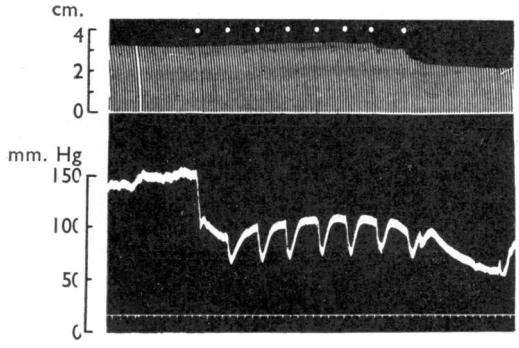

FIG. 1.—Record of the contractions of the tibialis anterior muscle and of the blood pressure before and after repeated intravenous injection of 5 mg./kg. of mecamylamine (at the white dots) into a cat anaesthetized with chloralose. Time, 30 sec.

and Downing (1947). In some animals the renal arteries were ligated to prevent loss of the drug in the urine during the experiment.

RESULTS

After the intravenous administration of 5 to 10 mg./kg. of mecamylamine there was an immediate and abrupt fall in blood pressure (Fig. 1) associated with bradycardia. This extreme hypotension was transient, and partial recovery, preceded by an increase in pulse rate, was observed within 1 min. A similar sequence of events succeeded each injection of mecamylamine. When the blood pressure was ultimately stabilized the degree of hypotension was invariably less marked than that initially observed.

Under normal circumstances there is an immediate rise in blood pressure when carbon dioxide is given to a cat, and this rise is sustained until the carbon dioxide is discontinued, when it falls sharply. In addition there is usually, but not invariably, a slight depression of the muscle twitch which is slower in onset than the hypertension and only gradually recovers when the inhalation of carbon dioxide is abandoned (Fig. 2).

After mecamylamine, instead of a rise the inhalation of carbon dioxide produced an acute fall in blood pressure (-34%, $P<0.001$); this fall was maintained until the administration of carbon dioxide was discontinued (Fig. 4), when the blood pressure rose and then gradually returned to the level at which it was stabilized after the injections of mecamylamine. Repeated administrations of carbon dioxide for short intervals became progressively less effective as the time interval lengthened after the injections of mecamylamine.

The preliminary intravenous injections of mecamylamine were followed almost at once by

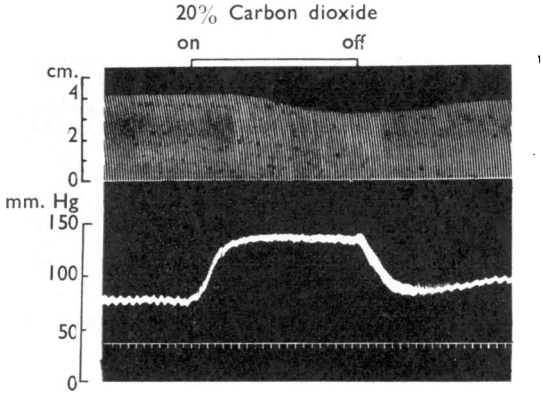

FIG. 2.—Record of the contractions of the tibialis anterior muscle and of the blood pressure before, during, and after the inhalation of 20% carbon dioxide by a cat anaesthetized with chloralose. Time, 30 sec.

a slight potentiation of the muscle twitch which was replaced by depression as the dosage was increased (Fig. 1). A depression to approximately 50% of normal was obtained with doses between 40 and 50 mg./kg. The inhalation of carbon dioxide increased the depression in all experiments (twitch decreased 48% $P<0.001$) as demonstrated in Fig. 3, and sometimes complete block was achieved. Since the effects of mecamylamine can be observed for some hours it was possible to demonstrate successive potentiation and recovery by intermittent administrations of carbon

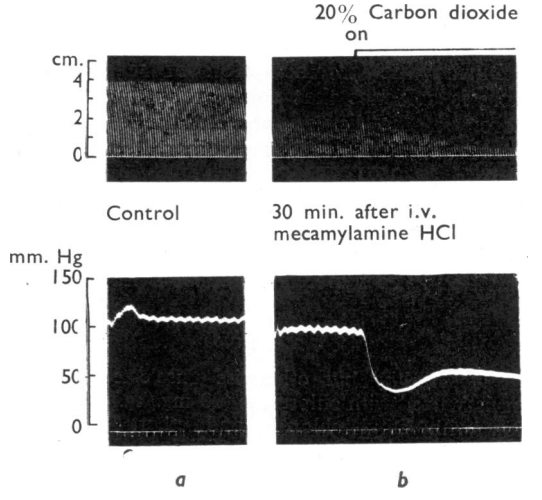

FIG. 3.—Record of the contractions of the tibialis anterior muscle and of the blood pressure in a cat anaesthetized with chloralose. *a*, Control records of the muscle twitch and blood pressure. *b*, 40 mg./kg. of mecamylamine was given intravenously 30 min. before the record was made. Note the effect of the inhalation of 20% carbon dioxide. Time, 30 sec.

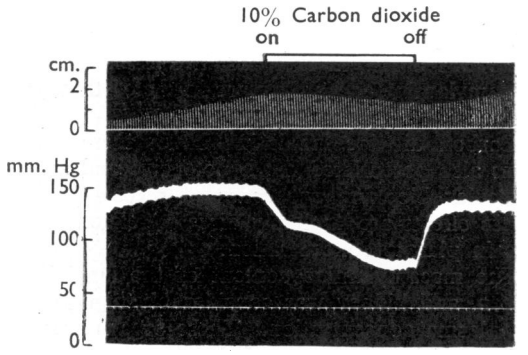

FIG. 4.—Record of the contractions of the tibialis anterior muscle and of the blood pressure in a cat anaesthetized with chloralose. 30 min. before this record was started, 40 mg./kg. of mecamylamine was given intravenously. Shortly afterwards the cat inhaled 10% carbon dioxide for a period and this record commences during the recovery from this procedure. A further inhalation of 10% CO_2, for a period shown above the tracing, again decreased the muscle twitch and lowered the blood pressure. Time, 30 sec.

dioxide for short intervals (Fig. 4). As with the effects on blood pressure, the potentiation of the neuromuscular block became less obvious as time passed after the administration of mecamylamine.

The mecamylamine content of liver, lung, spleen, kidney, brain, and muscle was estimated in several animals and the plasma and erythrocyte content in all. The lungs, liver, kidney, and spleen contained more mecamylamine than did blood, brain, and muscle; the amounts were roughly comparable to those found previously in the rat (Milne *et al.*, 1957).

Unfortunately, there are major technical difficulties in connexion with the extraction of mecamylamine from tissues, and since the reaction used is non-specific for secondary amines (Baer *et al.*, 1956) the tissue levels obtained varied considerably. In addition, the drug levels in the organs fell rapidly during the individual experiments, probably because of redistribution after the initial high concentration associated with intravenous injection (Milne *et al.*, 1957). The rate of fall in lung, liver, and kidney concentrations was so rapid that the influence of carbon dioxide on the mecamylamine content of these tissues could not be assessed. An attempt to minimize this complication was made by ligating the renal vessels; but even these experiments did not give clear-cut answers. A second difficulty was that repeated biopsies of the same organ were required; and it was hard to be sure that later samples were derived from organs with a satisfactory blood supply corresponding to the normal physiological state. The plasma and erythrocyte content alone yielded consistent and reproducible results, free from the foregoing criticisms.

In 17 separate estimations in nine cats given mecamylamine the average plasma mecamylamine content was 13.0 ± 5 μg./ml. After administration of carbon dioxide, the average rise in plasma mecamylamine was 5.0 μg./ml., with a standard deviation of ± 0.8 μg./ml. This increase was significant because it was consistent for each animal and the "*t*" test for paired values gave a *P* value <0.001. Since the erythrocyte content remained unchanged, the ratio of the content in erythrocytes to that in plasma fell from 1.12 to 0.83 ($P<0.001$).

DISCUSSION

It has been established that when cats previously given mecamylamine were ventilated with carbon dioxide the plasma level of the drug was raised substantially. Previous work (Milne *et al.*, 1957) has shown that the mecamylamine content of the liver, lung, kidney, and spleen becomes considerably higher than that of the blood, within minutes of its administration. Presumably the additional quantity demonstrated in the blood under the conditions of the experiments is mobilized from these organs by the action of carbon dioxide. This presumption is supported not only by the fact that the mecamylamine content of the organs fell during the experiments, but also by the established effects of *p*H on protein binding of drugs (Goldstein, 1949).

At the same time it was shown that the hypotension and neuromuscular block that follow the use of mecamylamine were potentiated during ventilation with carbon dioxide. The associated rise in plasma mecamylamine concentration may help to explain these effects. It is possible that mecamylamine is pharmacologically active only in the extracellular phase as has been postulated for hexamethonium and other ganglion blockers (Paton and Zaimis, 1952). If this is so, the high organ content of mecamylamine could serve as an inactive reservoir from which the drug becomes available in appropriate circumstances such as the presence of excessive carbon dioxide. This explanation would account for the smooth and sustained action curve of the drug as well as the potentiation of neuromuscular block and the extension of the hypotensive effect.

Although a rise in plasma mecamylamine levels has been demonstrated during carbon dioxide inhalation it does not follow that the increased hypotension produced is necessarily due to ganglionic blockade. If the autonomic ganglia are already paralysed completely, increased con-

centrations of mecamylamine will not produce any greater effect at these sites. An additional action must be postulated, and the transient bradycardia and hypotension that follow the intravenous injection of mecamylamine draw attention to one possibility—namely, a direct depressant action of the drug on the heart itself. This interpretation was suggested by the work of Bennett, Tyler, and Zaimis (1957), who have shown that in the isolated perfused heart the administration of mecamylamine can reduce the force of contraction and produce cardiac arrest.

It is, of course, conceivable that the additional hypotension was the result of a peripheral action of carbon dioxide on the vascular bed in the absence of a central effect of the gas, mecamylamine having inhibited the vasoconstrictor response by the paralysis of sympathetic ganglia. Support for this hypothesis is provided by the observation that potentiation of the hypotensive response could be obtained with carbon dioxide in cats during total spinal block (Payne, unpublished observation) and by Goodman and Gilman (1955), who claim that a similar depression occurs in man if carbon dioxide is administered during spinal anaesthesia or after extensive sympathectomy.

It was also observed that the moderate neuromuscular block obtained with mecamylamine was potentiated when the animal was exposed to carbon dioxide, and it is reasonable to conclude that this increase in block is due to the rise in the mecamylamine level of the plasma caused by the carbon dioxide. It could be argued, however, that the further depression of the muscle twitch is a direct effect of carbon dioxide and unrelated to the plasma level of mecamylamine. This is unlikely because, although carbon dioxide could depress the individual muscle twitch in the cat (Fig. 2), the effect was slight compared with that in the experiments described.

When cats previously given mecamylamine intravenously are ventilated with carbon dioxide there was a rise in the plasma concentration of mecamylamine and a decrease in the erythrocyte/plasma ratio.

Carbon dioxide inhalation under these conditions also potentiated the hypotensive and neuromuscular blocking properties of mecamylamine. These effects are probably directly related to the rise in plasma concentration.

The mecamylamine content of the lung, liver, spleen, and kidney was considerably higher than the plasma concentration. These organs presumably provide the source of the drug made available to the plasma by the action of carbon dioxide.

The authors are indebted to Professor W. D. M. Paton for facilities to carry out the experimental work and also for much valuable advice and criticism. Thanks are due to Dr. J. F. Merry, of Messrs. Merck, Sharpe and Dohme, for liberal supplies of mecamylamine, and to Miss Hedges, Mr. M. A. Crawford, and Mr. D. Green for their technical assistance. The financial cost of the work was met by a grant from the Dan Mason Research Foundation to one of us (J. P. P.).

References

Baer, J. E., Paulson, S. F., Russo, H. F., and Beyer, K. H. (1956). *Amer. J. Physiol.*, **186**, 180.

Bennett, G., Tyler, C., and Zaimis, E. (1957). *Lancet*, **2**, 218.

Brodie, B. B., Udenfriend, S., Dill, W., and Downing, G. (1947). *J. biol. Chem.*, **168**, 311.

Brown, G. L. (1938). *J. Physiol.*, **92**, 23P.

Goldstein, A. (1949). *Pharmacol. Rev.*, **1**, 102.

Goodman, L. S., and Gilman, A. (1955). *Pharmacological Basis of Therapeutics*, 2nd ed., p. 919. New York: Macmillan.

Milne, M. D., Rowe, G. G., Somer, K., Meuhrcke, R. C., and Crawford, M. A. (1957). *Clin. Sci.*, in the press.

Paton, W. D. M., and Zaimis, E. J. (1952). *Pharmacol. Rev.*, **4**, 219.

Stone, C. A., Torchiana, M. L., Navarro, A., and Beyer, K. H. (1956). *J. Pharmacol.*, **117**, 169.