Brit. J. Pharmacol. (1952), 7, 542.

THE FALL OF BLOOD PRESSURE CAUSED BY INTRAVENOUS MORPHINE IN THE RAT AND THE CAT

BY

A. G. J. EVANS, P. A. NASMYTH, AND H. C. STEWART

From the Department of Pharmacology, St. Mary's Hospital Medical School, London, W.2

(Received May 21, 1952)

In 1933 Schmidt and Livingstone attempted to determine the cause of the marked fall of blood pressure which results when morphine sulphate is injected intravenously into the cat or the dog. They showed that the phenomenon exhibited tachyphylaxis and that it was unaffected by ether, urethane, barbitone, or phenobarbitone. They were unable to arrive at any definite conclusions and could only suggest that " depression of the vasomotor centre plays some part in this effect, but most of it is due to dilatation of cutaneous and muscular blood vessels by direct action upon their walls."

Sollmann and Pilcher (1917) reported that morphine evoked the triple response in the human skin, an observation which was confirmed by Lewis (1927). Since that time Nasmyth and Stewart (1950) have shown that the weals caused by morphine in human skin are reduced by antihistamine drugs. Feldberg and Paton (1950) reported that the intra-arterial injection of morphine into the isolated perfused gastrocnemius muscle of the cat caused the appearance of histamine in the effluent, and later (Feldberg and Paton, 1951) showed that the drug also released histamine from the cat's skin and that after its intravenous injection into the intact animal the plasma histamine was raised. They considered that the fall of blood pressure caused by the intravenous injection of morphine could not be wholly accounted for by the release of histamine.

In this work we have shown that the effect is complex and that at least three factors which would affect the blood pressure are involved when morphine is injected intravenously.

METHODS

Anaesthesia.—All the rats from which records of blood pressure were taken were anaesthetized with urethane (7 ml./kg. of a 25 per cent (w/v) solution injected subcutaneously). Rats which received injections of morphine sulphate into the jugular vein 24 hours before records of blood pressure were taken from them were anaesthetized with ether while the vein was exposed.

Cats were anaesthetized with ether followed by 80 mg./kg. of chloralose intravenously.

Records of blood pressure.—All animals except decerebrate and spinal cats, from which records of blood pressure were taken, were heparinized. The apparatus described by Condon (1951) was used to record the blood pressure of the rats.

Collection of adrenal vein blood samples.—The samples of cats' adrenal vein blood were collected by the method described by Vogt (1943), except that the colon was not removed. The samples were placed on ice as soon as collection was completed.

Assay of pressor substances in adrenal vein blood samples.—The effects of injecting suitable volumes of the adrenal vein blood samples were compared with those produced by doses of adrenaline on the cat's blood pressure. The animals were pretreated with 0.5 mg./kg. of atropine sulphate intravenously, 5 mg./kg. of mepyramine maleate subcutaneously, and 3 mg./kg. of cocaine hydrochloride intravenously. Thirty minutes later 40 mg. hexamethonium bromide was given intravenously. The blood samples were assayed immediately after the dose of hexamethonium bromide.

Number of experiments.—Each experiment was repeated with similar results in not less than three animals unless otherwise stated.

Drugs.—Throughout this paper the doses for drugs refer to the following salts: morphine sulphate, histamine acid phosphate, hexamethonium bromide, mepyramine maleate, atropine sulphate, acetylcholine chloride, and nicotine hydrogen tartrate.

RESULTS

Intravenous injection of morphine in rats

Anaesthetized rats.—In the initial experiments 10 mg./kg. of morphine was injected into the jugular vein. This dose always produced a sharp transient fall in blood pressure lasting from 20 to 30 seconds. Upon repeating the injection the result varied from a less marked but equally transient fall to no effect; this tachyphylaxis occurred consistently. A third dose given shortly after the second was invariably without effect. It was subsequently found that 10 mg./kg. was an unnecessarily high dose and that similar responses could be obtained with doses of 1 mg./kg.

The fall of blood pressure caused by morphine was more transient than that caused by an equi-depressor dose of histamine. Whereas the response to morphine exhibited tachyphylaxis, the response to repeated injections of the same dose of histamine remained unchanged. This is illustrated in Fig. 1.

An attempt was made to determine the period during which the vasodepressor response to intravenous morphine was unobtainable after initial doses of the drug. It was found impossible to keep the rats in a suitable condition for experiment for longer than five hours when their blood pressure was being recorded from the

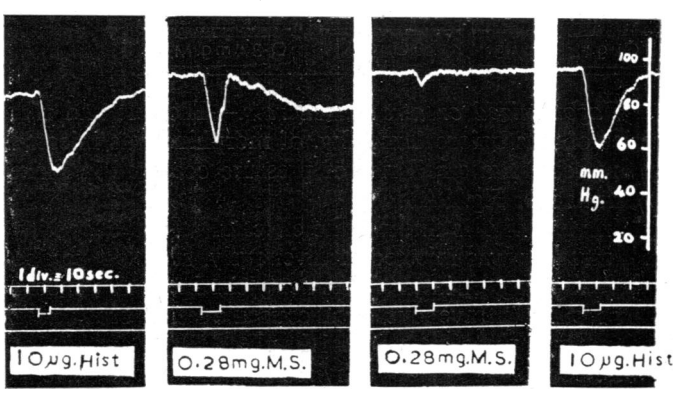


FIG. 1.—Rat: Urethane. The effect of repeated intravenous injections of 1 mg./kg. of morphine on blood pressure. The tracings run consecutively; parts of the record have been removed to condense the material. They show the transient response to morphine compared with the responses to histamine, when both are injected intravenously. Note the tachyphylaxis displayed by the response to morphine. Hist.=Histamine. M.S.=Morphine sulphate.

carotid artery, but in experiments covering this period, a further fall in blood pressure was only obtained once, and then only two hours after the first ineffective dose of morphine. It was concluded that the vasodepressor response is not generally repeatable until more than five hours have elapsed after the last effective dose of morphine.

A number of experiments were performed in which three 1 mg./kg. doses were injected into the exposed jugular vein with a three-minute interval between each dose. The wound was then sutured and the animal used 24 hours later to record blood pressure in the usual way. In all these animals a vasodepressor response was obtained when 1 mg./kg. of morphine was injected intravenously. It was concluded that the normal response to intravenous morphine in the rat, after the vasodepressor response has once been elicited, cannot be obtained until more than 5 but less than 24 hours have elapsed. It was noted that the second series of morphine injections causing falls in blood pressure also exhibited tachyphylaxis.

Rats treated with mepyramine.—Nasmyth (1951) showed that the subcutaneous injection of 5 mg./kg. of mepyramine into rats effectively blocked the fall of blood pressure caused by intravenously injected histamine for periods in excess of 3 hours. The same dose and route of injection were therefore employed in these experiments. The rat is relatively insensitive to histamine and intravenous doses of 10 μg. histamine were required to produce appreciable responses. Twenty to thirty minutes after the injection of mepyramine, no response could be obtained to the intravenous injection of 30 μg. histamine. The intravenous injection of 1 mg./kg. of morphine under these circumstances caused a fall of blood pressure which was more profound and less transient than that obtained in animals untreated with mepyramine. Typical records are shown in Fig. 2.

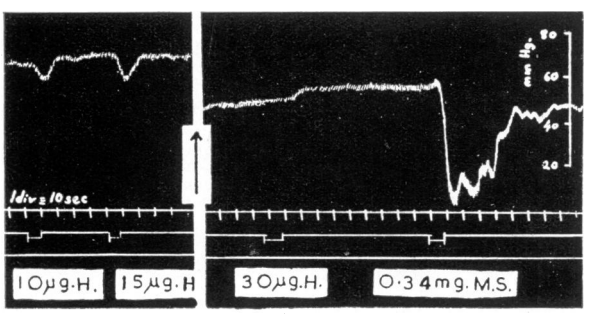


FIG. 2.—Rat: Urethane. The effect of mepyramine on the response of the blood pressure to 1 mg./kg. of morphine sulphate injected intravenously. At the arrow 5 mg./kg. of mepyramine was injected subcutaneously and the morphine was injected 30 minutes later. H=Histamine. M.S.=Morphine.

Vagotomized or atropinized rats.—The left and right vagi were sectioned in a series of rats before 1 mg./kg. of morphine was injected into the jugular vein. On each occasion a small rise of pressure occurred in place of the usual fall. This is illustrated in Fig. 3A.

In view of this finding, the effect of atropine was investigated. Accordingly 0.25 mg. atropine was injected intravenously, sufficient to abolish the blood pressure response to 5 mg. of intravenous acetylcholine. The subsequent injection of 1 mg./kg. of morphine intravenously still caused a fall of blood pressure, but the blood pressure did not return to its original level. Subsequent doses of 1 mg./kg. of morphine exhibited the usual tachyphylaxis in the hypotensive response. These effects are

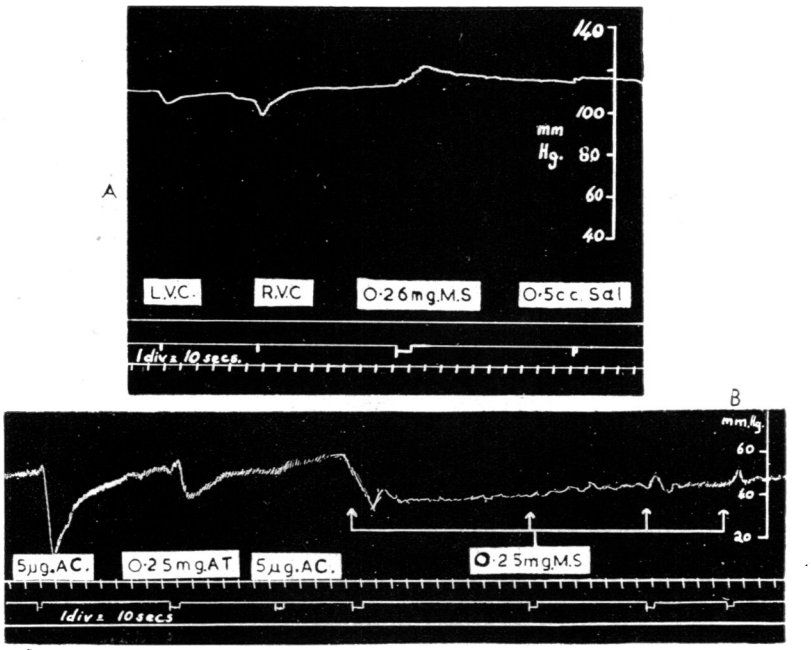


FIG. 3.—Rat: Urethane. The effect of the intravenous injection of 1 mg./kg. of morphine on blood pressure:—Tracing A—after cutting both vagi. Tracing B—after atropine. R.V.C.=right vagus cut. L.V.C.=left vagus cut. M.S.=Morphine. AC.=Acetylcholine. AT.=Atropine.

illustrated in Fig. 3B. • A dose of 2 mg. acetylcholine, after these doses of morphine, caused a rise in blood pressure which indicated that morphine had no effect on the action of acetylcholine on sympathetic ganglia.

Rats treated with hexamethonium.—The dose of hexamethonium required to produce ganglion block in rats was unknown. When the elevation of blood pressure produced by the intravenous injection of 0.1 mg. nicotine was used as a criterion, it was found that 60 mg./kg. of hexamethonium was required to produce ganglion block. Under these circumstances responses to intravenous injections of morphine were blocked at dose levels of 1 mg./kg. and at 10 mg./kg. The result is illustrated in Fig. 4.

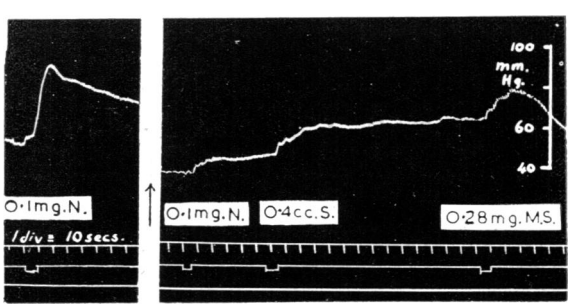


FIG. 4.—Rat: Urethane. The effect of the intravenous injection of 1 mg./kg. of morphine on blood pressure after 60 mg./kg. of hexamethonium given intravenously (at the arrow). N=Nicotine. S=Normal saline. M.S.=Morphine.

The intravenous injection of morphine in cats

Anaesthetized cats.—The effect of intravenously injected morphine on the cat's blood pressure differs in some respects from the effect obtained in the rat. Pilot experiments indicated that a fall of pressure was sometimes obtained when 2 mg./kg. of morphine was injected into the jugular vein, but that 4 mg./kg. was always effective.

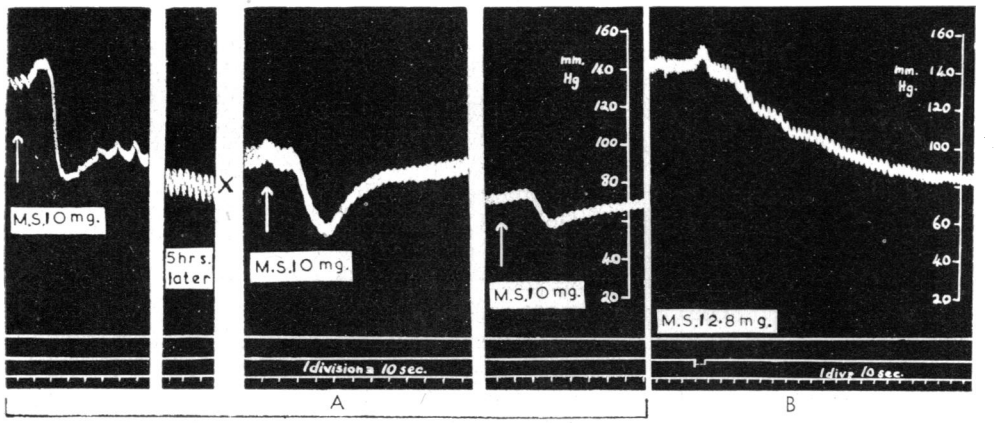
The intravenous injection of the latter dose caused a transient rise in pressure followed by a precipitous fall 15 to 20 seconds after completion of the injection. During the first 2 or 3 minutes after the injection, the heart rate increased slightly but was subsequently slower than normal. After the pressure had fallen, it did not recover during the next seven hours. The infusion of 50 ml. of 3.5 per cent polyvinylpyrrolidone at 37° C. at the end of this period served to raise the pressure only a little. A second dose of 4 mg./kg. of morphine then caused a transient fall in pressure. A third dose gave a yet smaller response. At this dose level the respiration was always inhibited, and sometimes failed, but whether artificial respiration was employed or not the fall in blood pressure was constant.

When doses of 20 mg./kg. were injected intravenously in anaesthetized cats, the pattern of the blood pressure response was identical with that obtained with a dose of 4 mg./kg. With the larger dose the fall in pressure was more profound, often to 20 or 30 mm. of mercury, but within 2 hours it had risen and remained at a level corresponding with that to which the pressure usually fell with the smaller dose. Repetition of the dose of morphine under these circumstances produced transient and gradually diminishing responses. The respiration always failed when 20 mg./kg. of morphine was injected intravenously.

Decerebrate cats.—In the decerebrate cat, the intravenous injection of 4 mg./kg. of morphine caused a fall of blood pressure which was less precipitous but just as profound as that produced by the same dose of the drug in the anaesthetized cat. The effect was of shorter duration, lasting 10 to 15 min., and exhibited the usual tachyphylaxis on repeated injections. In these animals the respiration never failed and was rarely more than very slightly depressed.

Spinal cats.—When 4 mg./kg. of morphine was injected intravenously in the spinal cat, the fall in blood pressure was precipitous, but less profound than in the anaesthetized cat, presumably because the vasomotor tone was lower. Within 40 sec. of completion of the injection the pressure began to rise, and after 70 sec. it had returned almost to the initial level. The initial pressure level was usually regained within 15 min., and a second dose of 4 mg./kg. of morphine then gave a similar but smaller effect and repeated dosage with morphine eventually abolished it. In one animal the fall in blood pressure disappeared after five injections of morphine given during a period of 80 min., but when a sixth injection of morphine was given, 30 min. after the fifth, a typical fall of pressure was obtained. In another spinal animal the initial pressure was only 45 mm. of mercury, and in this instance morphine produced no blood pressure response. The effects of the intravenous injection of 4 mg./kg. of morphine in anaesthetized, decerebrate, and spinal cats are illustrated in Fig. 5.

Cats treated with mepyramine.—A dose of 5 mg./kg. of mepyramine was injected subcutaneously into anaesthetized cats. Usually it blocked the depressor response to doses of histamine ranging from 1 to 5 μg. 30 min. after the administration. A few



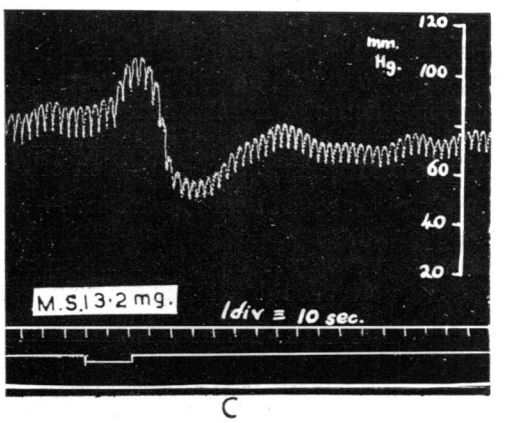


FIG. 5.—The effects on blood pressure of 4 mg./kg. of morphine injected intravenously in the cat. (A) Anaesthetized cat (chloralose): 50 c.c. of polyvinylpyrrolidone (3.5 per cent) was infused at X. There was an interval of 5 min. between the last two doses of morphine. (B) Decerebrate cat. (C) Spinal cat. M.S.= Morphine.

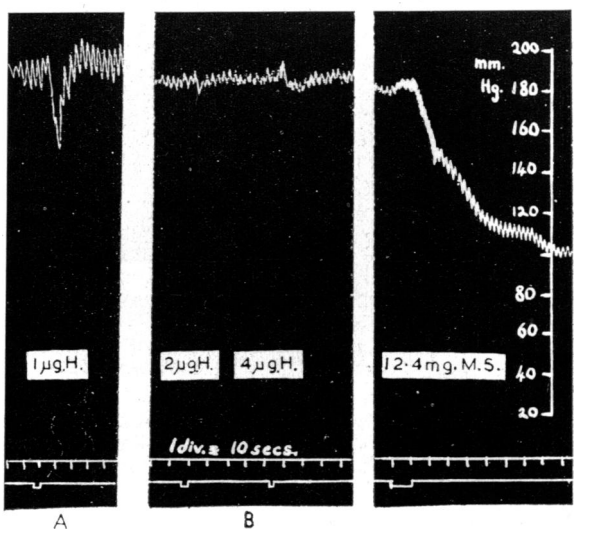


FIG. 6.—Cat: Chloralose. The effect of mepyramine on the fall of blood pressure caused by injecting 4 mg./kg. of morphine intravenously. There was an interval of 30 minutes between (A) and (B), at the commencement of which 5 mg./kg. of mepyramine was injected subcutaneously. H = Histamine. M.S.= Morphine.

animals were resistant to mepyramine and even intravenous injection of the drug failed to block the blood pressure response to histamine. These animals were discarded.

After an effective dose of mepyramine maleate, 4 mg./kg. of morphine sulphate injected intravenously always produced a profound and prolonged fall of blood pressure.

In two decerebrate cats similarly pretreated with mepyramine the pressure fell when 4 mg./kg. of morphine was injected intravenously, but the magnitude of the response was less than half that normally obtained in decerebrate cats. In a third animal pretreated with mepyramine, the intravenous injection of 4 mg./kg. of morphine sulphate produced no response. The effect in the spinal cat was always completely blocked by pretreatment with mepyramine.

The effect of intravenously injected morphine in the anaesthetized cat pretreated with mepyramine is illustrated in Fig. 6.

Atropinized and vagotomized cats.—In order to determine the effect of atropine on the phenomenon the left vagus was cut and the effect of stimulating the peripheral cut end was investigated ; 5 mg. atropine was then injected, and, after a few minutes, stimulation of the peripheral cut end of the left vagus was without effect. The injection of 4 mg./kg. of morphine then caused the usual fall of blood pressure and it remained low for two hours. In cats with both vagi cut, the pattern of the response to an intravenous injection of 4 mg./kg. of morphine was not modified.

Cats treated with hexamethonium.—The intravenous injection of 0.1 mg. nicotine produced a steep rise in blood pressure. After a dose of 40 mg. hexamethonium intravenously, injection of 0.3 mg. nicotine gave no pressor response ; this was taken as evidence that the autonomic ganglia were effectively blocked. A dose of

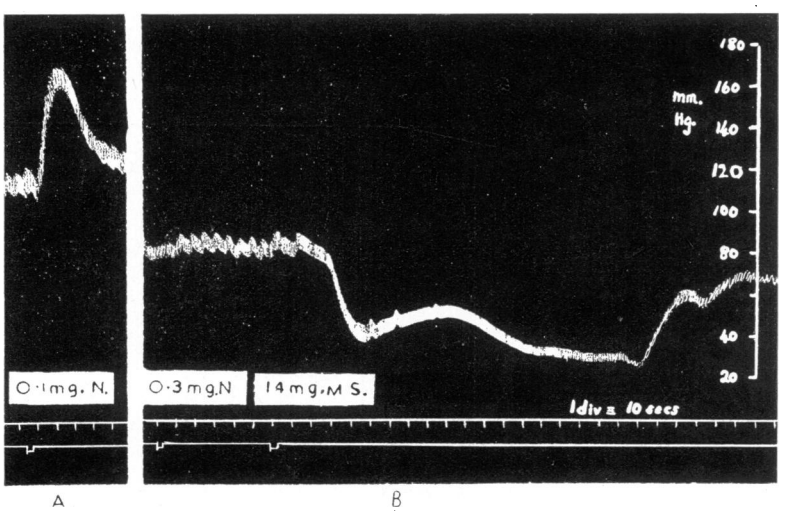


FIG. 7.—Cat: Chloralose. The effect of hexamethonium on the fall of blood pressure caused by injecting 4 mg./kg. of morphine intravenously. During the interval between (A) and (B) 10 mg./kg. of hexamethonium was injected intravenously. N=Nicotine. M.S.=Morphine.

4 mg./kg. of morphine now caused a precipitous fall in blood pressure, which in two experiments was more transient than that normally obtained. In one animal the pressure had returned to a level only 10 mm. of mercury below the initial value within four minutes (Fig. 7). The effect in the second animal was similar, but it was twelve minutes before the pressure approximated to the normal value. In the third animal the injection of morphine caused the usual fall in blood pressure, which remained low. In this series of experiments 4 mg./kg. of morphine almost invariably stopped the respiration.

It seemed possible that the more transient fall in blood pressure obtained in the presence of hexamethonium could be due to histamine released from tissues. In order to test this point, a series of experiments was performed in which the animals were pretreated with mepyramine and hexamethonium. The responses to 0.1 mg. nicotine and 2 μg. histamine were first demonstrated; thereupon 5 mg./kg. of mepyramine was injected subcutaneously, followed by 40 mg. hexamethonium intravenously thirty minutes later. Repetition of the doses of nicotine and histamine then produced no change in the blood pressure. Following this, 4 mg./kg. of morphine injected intravenously caused a very slow fall in blood pressure as shown in Fig. 8.

Pressor substances in the adrenal vein blood after intravenous morphine

The preliminary rise of blood pressure which was always observed when morphine was injected into anaesthetized, but otherwise untreated, cats suggested that there might be a considerable release of pressor substances from the adrenal medulla. Consequently, an experiment was performed in which the total pressor activity of

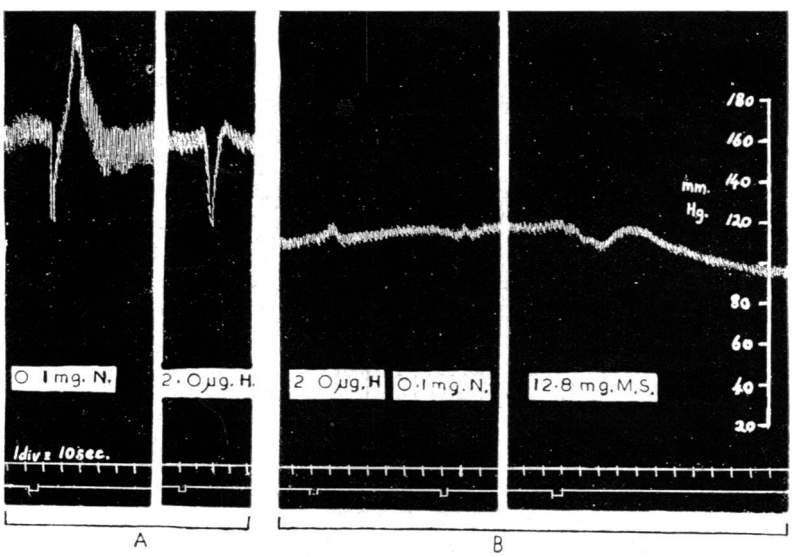


FIG. 8.—Cat: Chloralose. The effect of hexamethonium and mepyramine on the fall of blood pressure caused by injecting 4 mg./kg. of morphine intravenously. There was an interval of 30 minutes between A and B, at the commencement of which 5 mg./kg. of mepyramine was injected subcutaneously. At the end of this period, 10 mg./kg. of hexamethonium was injected intravenously. N=Nicotine. H=Histamine. M.S.=Morphine.

TABLE I

The pressor activity (in terms of μg. of *l*-adrenaline per ml.) of cat's adrenal vein blood samples before and after the intravenous injection of morphine. Collection of the first sample after morphine began immediately, and there were no intervals between the collection periods of the following samples.

Cat	Sample volume (ml.)	Dose of morphine (mg./kg.)	Collection period (min. sec.)	Pressor activity (μg. adrenaline per ml.)
A	5.0	—	2 20	0.25
	2.5	4	5 10	1.74
	5.0	4	3 45	3.73
	5.0	4	3 20	2.40
B	5.0	—	1 5	0.31
	5.0	4	2 28	3.80
	5.0	4	4 15	2.00
	5.0	4	3 20	1.70
C	5.0	—	1 35	0.20
	5.0	4	3 35	2.00
	5.0	4	3 0	2.00
D (Control)	5.0	—	1 20	0.40
	5.0	—	1 5	0.40
	5.0	—	1 10	0.60
	5.0	—	1 23	0.45

adrenal vein blood samples was assessed before and after an intravenous injection of 4 mg./kg. of morphine.

The samples of adrenal vein blood were collected and assayed as already described. With one exception the volume of each sample was 5 ml. The results obtained are shown in Table I. In each of the cats A, B, and C, one sample was collected after a control injection of normal saline; 4 mg./kg. of morphine was then injected into the jugular vein and the collection of further samples started immediately. It will be noted that in these cats the collection periods and the pressor activity of the samples were increased after the injection of morphine. In cat A, the collection period of the first sample after the injection of morphine was so much increased that only 2.5 ml. had been obtained in 5 min. and 10 sec.

In order to determine the effect of withdrawing 20 ml. of blood on the pressor activity of the adrenal vein blood, an experiment was performed in which four 5 ml. samples were collected without the injection of morphine. The results obtained in this experiment are shown for cat D. It will be observed that neither the pressor activity nor the collection period of the samples was significantly altered.

Discussion

The observations of Schmidt and Livingstone (1933) on the depressor effect of intravenous morphine on the cat's blood pressure have been confirmed and extended.

In the spinal cat the intravenous injection of 4 mg./kg. of morphine caused a small transient rise in blood pressure followed by a precipitous fall from which recovery was complete within fifteen minutes, and the phenomenon was shown to exhibit tachyphylaxis on repetition of the dose. The effect could not be obtained in animals with a pressure lower than 60 mm. Hg. In cats anaesthetized with chloralose the

pattern of the response was the same as that in the spinal cat, except that the fall in pressure was more profound and persisted for longer than five hours. This difference suggested that either the anaesthetic or the medullary and hypothalamic centres contributed to the effect in the anaesthetized animal. In the decerebrate cat the fall of blood pressure caused by morphine was less precipitous than, but equally profound as, that in the anaesthetized animal. It was, however, of shorter duration, lasting only 10–15 minutes. The similarity in the duration of the effect in spinal and decerebrate cats and the prolongation of the phenomenon in animals under chloralose suggested that the anaesthetic either potentiated the blood pressure lowering effect of the morphine or inhibited compensatory mechanisms.

Though morphine is known to release histamine from cat's skin and muscle, pretreatment of anaesthetized animals with mepyramine did not alter the response of the blood pressure to intravenously injected morphine, whereas similar pretreatment of spinal and decerebrate cats either abolished or considerably reduced the response. The inference was that the phenomenon in the spinal and decerebrate cats was mediated by histamine released in the animal's tissues, and that any central actions of morphine affecting blood pressure were compensated. The ineffectiveness of mepyramine in the anaesthetized cat suggested that morphine had some central action which was potentiated either by the anaesthetic or by vasomotor effects that were uncompensated in its presence.

The observation in two experiments that pretreatment of anaesthetized cats with hexamethonium did not abolish the fall in blood pressure, but reduced its duration to a time comparable with that seen in spinal and decerebrate animals, may indicate that morphine has some effect on central vasomotor mechanisms. It is interesting to note that this period corresponds closely with the time during which plasma histamine is increased after morphine injection (Feldberg and Paton, 1951). It was also shown that pretreatment of anaesthetized animals with both mepyramine and hexamethonium abolished the typical response of the blood pressure to intravenous morphine.

Some indication of the nature of the central effect was obtained from the observations that neither pretreatment with atropine nor bilateral vagotomy affected the pattern of the response to intravenous morphine in the anaesthetized cat. The additional observation, that the heart rate was increased during the first two or three minutes after a dose of morphine, also contributes to the supposition that the central actions of morphine which affect the circulation are on the vasomotor rather than the vagomotor centre.

Schmidt and Livingstone (1933) reported that morphine did not lower the blood pressure of the rat under ether, yet they show a kymograph tracing depicting an exactly similar fall of pressure to that reported by us. In addition to being different in character from the response in the cat, the response in the rat is also different in nature, since it is blocked by hexamethonium bromide and by bilateral vagotomy, but not by atropine. The inference would appear to be that the effect of intravenous morphine on the circulation of the rat is mediated by sensory impulses in the vagus nerve.

It was shown by Elliott (1912), and confirmed by Emmelin and Strömblad (1951), that morphine depletes the adrenal medulla of its content of pressor substances. The latter authors also showed that ether and chloralose anaesthesia had a rela-

tively small effect. The cats in which the pressor content of adrenal vein blood samples was assayed were pretreated with an antihistamine and atropine, as it had been shown by Schmiterlow (1951) that the presence of acetylcholine or histamine in samples to be assayed for pressor activity materially affects the result. Schmiterlow (1951) also recommended the removal of the adrenal glands from the test animal in order to prevent the release of pressor substances by contaminants which may be present in the samples. In the foregoing experiments the test animal was pretreated with hexamethonium which, at one and the same time, prevented the release of pressor substances and helped to make the animal more sensitive to those injected.

SUMMARY

1. The intravenous injection of 4 mg./kg. of morphine causes a profound and prolonged fall of blood pressure in the cat anaesthetized with chloralose. The effect occurs, but is modified, in decerebrate and spinal cats. The effect in the rat anaesthetized with urethane is transient, it exhibits tachyphylaxis, and can be obtained with doses as low as 1 mg./kg. Once the effect has been exhausted in the rat, it can be repeated after 24 hours have elapsed.

2. The effect is not blocked by mepyramine in either anaesthetized cat or rat. In the spinal cat the effect is completely blocked by mepyramine, and in the decerebrate cat it is very much reduced.

3. Hexamethonium bromide prevents the effect in the rat. It sometimes modifies, but never blocks, the effect in the anaesthetized cat. The combination of hexamethonium and mepyramine minimizes the response in the cat.

4. Atropine does not prevent the response in either the rat or the cat.

5. Cutting the vagi abolishes the effect in the rat but not in the cat.

6. The content of pressor substances in adrenal vein blood samples from the cat is increased 10 to 15 times after the intravenous injection of 4 mg./kg. of morphine and remains high for at least 12 minutes after the injection.

7. It is concluded that the activity of intravenously injected morphine on the circulation of the cat is mediated largely, if not entirely, by an effect on the vasomotor centre and by the release of histamine peripherally. There is some compensation by increased secretion from the adrenal medulla. In the rat the effect appears to be mediated wholly by sensory impulses in the vagus nerve.

Our thanks are due to Professor Buttle, of the School of Pharmacy, for the loan of the Condon apparatus for recording rat blood pressures, and to Messrs. May and Baker Ltd. for generous supplies of polyvinylpyrrolidone and " Anthisan," and to the Sir Halley Stewart Trust for their continued financial support.

REFERENCES

Condon, N. E. (1951). *Brit. J. Pharmacol.*, **6**, 19.
Elliott, T. R. (1912). *J. Physiol.*, **44**, 374.
Emmelin, N., and Strömblad, R. (1951). *Acta physiol. scand.*, **24**, 261.
Feldberg, W., and Paton, W. D. M. (1950). *J. Physiol.*, **111**, 19*P*.
Feldberg, W., and Paton, W. D. M. (1951). *J. Physiol.*, **114**, 490.
Lewis, T. (1927). *The Blood Vessels of the Human Skin and their Responses*. London: Shaw & Sons.
Nasmyth, P. A. (1951). *J. Physiol.*, **112**, 215.
Nasmyth, P. A., and Stewart, H. C. (1950). *J. Physiol.*, **111**, 19*P*.
Schmidt, C. F., and Livingstone, A. E. (1933). *J. Pharmacol.*, **47**, 411.
Schmiterlow, C. G. (1951). *Brit. J. Pharmacol.*, **6**, 120.
Sollmann, T., and Pilcher, J. D. (1917). *J. Pharmacol.*, **9**, 309.
Vogt, M. (1943). *J. Physiol.*, **102**, 341.