# MORPHINE AND HISTAMINE RELEASE

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A wide range of drugs exert analeptic action in dogs treated with morphine; cyclizine, diphenhydramine, chlorcyclizine, Avil, tripelennamine and succinic acid. Benactyzine and Pacatal are without effect. Histamine and an antihistaminase (isoniazid) exert some alerting action in a morphine-treated dog. Morphine induces the signs of histamine release in some dogs. Histamine itself reproduces some of the side effects of morphine. Histamine-treated dogs appear to be analgesic. Rabbits and dogs, behaved similary but cats were different and variable when given antihistamine drugs after morphine. Some of the side actions of morphine are mediated by histamine release.

ONE serious side action of morphine, in addition to respiratory depression, is the production of nausea and vomiting. A recent survey[1] found the incidence in healthy volunteers to be as high as 30 per cent. Emesis is much less frequent in the presence of pain. The incidence of vomiting is not reduced by the use of nalorphine nor by amiphenazole[1].

In an attempt to evaluate the stimulant effect of amiphenazole on the mental depression brought about by morphine in man, the authors endeavoured to suppress the nausea, which interfered with the psychological testing, by the use of an anti-emetic, cyclizine chloride (Marzine). This weak antihistamine drug successfully prevented the nausea and vomiting but unexpectedly antagonised some of the actions of morphine. A description of the clinical observations will be published elsewhere[1]. As a result we investigated the action of certain antihistamine substances and other drugs on morphine-induced narcosis in animals.

The fact that morphine and pethidine could bring about the liberation of histamine under certain conditions had been shown previously by Feldberg and Paton[2], Nasmyth and Stewart[3], and Finer and Partington[4]. Three drugs have been used clinically to antagonise the narcotic effects of morphine, nalorphine[5], *N*-allyl-norcodeine[5] and amiphenazole[6]. There are in addition a number of compounds which can overcome the narcotic action in dogs[7,8]. To the above compounds, there must now be added a new series, of which the main members have antihistamine activity.

We employed three groups of drugs.

*Antihistamine Drugs*: Cyclizine hydrochloride, diphenhydramine hydrochloride, chlorcyclizine hydrochloride, *p*-amino salicylate of 1-phenyl-1-pyridyl-(2)-3-dimethyl-amino-propane (Avil) and tripelennamine.

*Tranquilising Drugs*: Benactyzine hydrochloride, and *n*-methyl piperidyl-(3)-methyl phenothiazine (Pacatal).

*Stimulants*: Methylphenidate and succinic acid in 10 per cent solution.

## METHOD

Healthy mongrel dogs of both sexes were given morphine, 10 mg./kg., and sometimes hyoscine (0·5 mg./kg.) intramuscularly. This caused

deep narcosis with complete analgesia so that minor surgery could be performed; the animals did not respond to marked stimuli, such as pricking with a needle or pressure on a limb. Onset was within approximately 20 minutes and lasted for at least 8 hours. Resistance to morphine was occasionally encountered, usually in the absence of hyoscine. No animal was used unless a deep sleep was obtained. It was observed that further doses of the narcotic seldom increased the depth of sleep. The phenomenon of resistance was investigated further in an attempt to correlate our observations and histamine-release; and in these experiments histamine was administered in a dose of 1 mg./kg.

The analeptic substances under test were given at the height of the morphine effect, 1–1¼ hours after the first morphine injection. These were usually given intravenously; some were intramuscular and a few intraperitonealy.

The animals were observed for signs of arousal for approximately one hour, and if these appeared they were watched for four hours or more in case there was a relapse to unconsciousness. Since the narcosis produced by the morphine or morphine with hyoscine was not always of a uniform depth, assessment of the effect of the compounds under investigation must of necessity be subjective. The effects were recorded as *good arousal* when the animal became alert, sat up and walked voluntarily, as *definite arousal*, when the animal sat up of its own accord, but walked only when called or gently moved, and *inactive* when there was no change in behaviour.

Additional experiments were made on rabbits, cats, and rats.

## Results

*Analeptic Action in Dogs.* The results with cyclizine, chlorcyclizine and Avil have been previously recorded[8], and are included for completeness.

Chlorcyclizine, 10 to 30 mg./kg., caused *definite arousal* in 9 of 10 dogs and was *inactive* in one. The animals were alert, but unable to stand. A minimal or absence of effect was seen on respiration. The dogs remained analgesic and did not withdraw their hind limbs when a painful stimulus was applied. They relapsed to their previous level of narcosis within about one hour.

Diphenhydramine, 20 to 25 mg./kg., was given i.v. in two and i.p. in one dog. There was a return to consciousness with minimal effect on respiration. The dose of 25 mg./kg. produced convulsions 5 minutes after injection. The dogs still showed muscular hypotonia and some uncoordinated movements, and could get up and move clumsily in response to stimulus. The animals remained analgesic and relapsed to the previous level after 1 to 2 hours.

Chlorcyclizine, 10 to 30 mg./kg., was given to nine dogs, i.m. in one. The response to injection was an immediate return to consciousness with an improvement in respiration in some. The muscles were still hypotonic. Doses of 25 and 30 mg./kg. produced prolonged and severe convulsions in three morphinised animals, ending fatally in one. Relapse occurred within ½ to 1½ hours, when the animals appeared quite anaesthetised, reverting to the pre-chlorcyclizine level.

Pyribenzamine, 10 to 20 mg./kg., was given to three dogs. After injection there was a return to a normal level of consciousness followed in all cases by gross extension and flexion spasms which lasted 20 minutes. One animal given 20 mg./kg. developed major convulsions and required the administration of barbiturate to counteract this effect. No effect was observed on respiration or analgesia and all relapsed to their previous level of narcosis within one hour.

Avil, 20 to 30 mg./kg., was given to 5 dogs. There was an immediate response with a return to full consciousness in all. Respiration and general muscle tone improved only slightly and they relapsed to their previous level after one hour.

Benactyzine, 0·33 mg./kg., was given to two dogs without effect.

Pacatal, 9 mg./kg., was given to one dog. The injection was followed by a deepening of coma and the animal remained narcotised for a longer period than the controls.

Methylphenidate, 2 mg./kg., was given to two dogs. There was an immediate return to a normal level of consciousness and there was some improvement in muscle tone. In one, respiration appeared to be impaired and in the other it was further depressed. They remained fully awake for about one hour after the injection.

Succinic acid 10 per cent was given to three different groups of animals.

1. Seven dogs were given 5 to 20 ml. i.v. There was a slight improvement in the level of consciousness in all. This consisted of an increased ability to recognise their surroundings and respond to the observer, but in most the animal was unable to get up and walk about, and remained analgesic. The respiration was markedly and consistently improved in all. No other analeptic tested was as active as succinate on respiration.

After about one hour the condition of the animals began to relapse, but they remained in a better condition than the controls.

2. A group of three dogs to which succinate was given as a resuscitative measure, one of which is briefly described. The dog was given morphine then 15 mg./kg. of cyclizine; after this the animal relapsed completely after one hour. Six ml. of 10 per cent succinic acid was then given intravenously and immediately produced a marked improvement in respiration and to a lesser degree in the level of consciousness.

3. Two dogs to which the succinate was given after the dose of morphine, but before the onset of narcosis. A dose of 10 ml. of succinic acid solution was given intraperitoneally 15 minutes after the morphine injection. The onset of morphine effects was not delayed, but the level of consciousness was appreciably better than in the control animals, also respiration was never depressed to the same degree as in the controls.

*Effect of Histamine in Dogs*

In these experiments 1 mg./kg. of histamine was administered i.v. to six morphinised dogs at various stages of the resultant narcosis. We also attempted to depress histaminase (diamine oxidase) action by injections of isoniazid[9].

1. A group of four dogs was given morphine and hyoscine mixture intramuscularly, and 1 mg./kg. histamine intravenously at the same time.

In all an extremely rapid onset of drowsiness and impairment of sense of balance was seen within two minutes after injection; this was followed within 10 to 20 minutes by complete loss of consciousness and muscle tone. All dogs showed signs of distress and "anxiety" during the injection of histamine; they also vomited, urinated and defecated. In one a short period of violent hyperactivity was observed, followed by a subdued, and finally inert condition.

The duration of narcosis was observed in two animals only, the others being given 30 mg./kg. Avil intravenously. This effected an improvement in the level of consciousness and respiration, which was very markedly depressed. The simultaneous treatment with histamine and morphine causes no significant changes in the duration of morphine narcosis. The onset of narcosis was much more rapid than usual, and the initial depth of narcosis was significantly deeper in all.

2. Two dogs were morphinised, and 1 mg./kg. histamine was injected intravenously one hour later. In both an immediate marked improvement in level of consciousness and muscle tone was observed, in addition general oedema and asthmatic respiration was seen.

This improvement was noticeable only for about five minutes after injection, but the dogs never relapsed completely to the level of consciousness of the controls, and were alert and normally active before the controls, that is at $4\frac{1}{2}$ to 6 hours after morphinisation. No effect was noted on respiration, apart from the transient "asthma".

3. Four dogs were treated with isoniazid.

(*a*) Two animals were given isoniazid alone, in doses of 30 and 45 mg./kg. intraperitoneally. The larger dose causes slight hyperactivity lasting about $1\frac{1}{2}$ hours, the smaller showed no apparent effect on the animal.

(*b*) One dog was given 30 mg./kg. isoniazid intraperitoneally, followed at once by normal morphinisation. For about $\frac{1}{4}$ hour, the dog was normally active, and was able to eat, but it collapsed suddenly and dramatically to a condition resembling the control, and one hour later was even further depressed in its general level of consciousness.

(*c*) One dog was morphinised and 30 mg./kg. isoniazid was injected intraperitoneally about $\frac{1}{4}$ hour later, before onset of morphine narcosis—the level of consciousness appeared similar to that of the control, being initially better, then becoming depressed.

Some transient oedema was noted soon after the injection of isoniazid; the dog recovered at the normal time after the initial morphinisation.

4. Two dogs were given 10 mg./kg. morphine and 0·5 mg./kg. hyoscine twice, intramuscularly.

(*a*) One animal was morphinised, and allowed to return to normal level of consciousness, about 6 hours later, when a second dose of morphine was injected. Slight drowsiness ensued, but the dog was always easily roused. Within ten minutes of the second treatment with morphine, general oedema of the tissues was noted, which lasted more than two hours.

(*b*) A second dog was morphinised, and was given a second dose of morphine one hour later. No apparent change in consciousness, muscle tone or respiration was observed.

These results may be summarised.

1. Histamine given before morphine narcosis appears to increase the rapidity of onset without affecting time of recovery. If injected during this narcosis histamine appears to improve the level of consciousness, and shorten the duration of effect of morphine.
2. Repeated morphinisation after short periods of 1 to 6 hours shows a decrease in effects of oedema and depression of consciousness which are more noticeable as the period between the doses decreases. This corresponds to the known effect on the blood pressure. This tachyphylaxis has been commented upon by Shaw and Bentley[10].
3. Isoniazid injected at same time as, or after morphine, causes an initial improvement in level of consciousness over that in the control, followed by a sudden and dramatic collapse, almost complete loss of consciousness and muscle tone occurring within 2 to 5 minutes. The recovery time is not affected.
4. Histamine in a dose of 1 mg./kg. i.v. causes disturbances in behaviour similar to those caused by morphine. These are, vomiting, defecation, loss of balance, and finally in some animals, drowsiness, in the initial stage of which the dogs were rousable. The animals appeared to be analgesic. Respiratory embarrassment was a common feature.

*The Effects of Histamine in Cats*

Morphine, 10 to 25 mg./kg., with hyoscine 0·5 to 1·2 mg./kg., was given i.v. (once i.m.) to 5 cats. Two were given Avil, 6 and 20 mg./kg., i.p. about one hour after morphine and hyoscine.

(i) *Morphine and Hyoscine without Avil.* Two cats were given 10 mg./kg. morphine intramuscularly and intraperitoneally respectively, and one cat 20 mg./kg. morphine injected intraperitoneally.

All showed bewilderment. One showed hyperactivity, which occurred about one hour after intramuscular injections of morphine, and lasted about one hour. There was minimal respiratory depression.

(ii) *Morphine and Hyoscine with Avil.* (*a*) Morphine, 20 mg./kg., with hyoscine injected intraperitoneally, no hyperactivity noted. Avil, 20 mg./kg., injected intraperitoneally one hour after morphine caused respiratory depression and fatal muscular tremors, without affecting activity. (*b*) Morphine, 25 mg./kg., with hyoscine injected intraperitoneally, no hyperactivity noted. One hour later Avil, 6 mg./kg., injected intraperitoneally produced no effect on the general level of consciousness, but slight muscular spasms were noted.

(iii) *Histamine.* Two cats were given histamine 5 mg., intravenously, and 9 mg./kg. respectively. The dosage of 5 mg./kg. produced severe shock and asthma, while that of 9 mg. caused some disturbance of the behaviour, but no shock.

The results may be summarised. The effect of morphine on cats is a variable bewilderment response, with hyperactivity in some. The only

antihistamine used as treatment showed no apparent effect on the morphine syndrome, but had fatal side-effects at doses found to be safe in dogs. It is possible that the results with the antihistamine drugs obtained with cats were at variance with those found in dogs because morphine affects cats differently.

*The Effect of Morphine on Rabbits*

Morphine, 8·3 mg./kg., was given 5 to rabbits intravenously; when drowsy an antihistamine drug was injected intravenously; in one rabbit the antihistamine drug was given before, and again after the morphine.

Avil, 5 mg./kg., was given intravenously to two rabbits; they became more active and moved about freely in the cage, but after an hour reverted to their previous condition, but were not analgesic. In one, Avil, 5 mg./kg., was given i.v. first, then morphine, 16·7 mg./kg. The animal became drowsy; a second injection of Avil, 5 mg./kg., was then given and the animal began to move about and explore its cage.

Cyclizine, 4 mg./kg., was given i.v. to two animals. They became active and started to walk about their cage but the drug was not analgesic. These animals remained active for about 1½ hours.

The effect of antihistamine drugs on the morphine-induced narcosis in rabbits is a temporary recession, similar to that in dogs.

The only other compound which calls for comment is succinic acid.

Succinate was given to a total of 18 dogs that were previously given morphine. In each, the respiratory depression was markedly and consistently improved. This response to succinate was more marked than with any other agents. The effect on respiration was mainly an increase in depth and to a lesser extent in rate. There was also a slight improvement in the level of consciousness, consisting mainly of an increased ability to recognise their surroundings and respond to the observer, but most of the animals were unable to get up and walk about. A similar response has been observed in barbiturised animals[14]. Barrett[15] found that succinate was an effective analeptic in the treatment of morphine poisoning in man. This has also been observed in this laboratory by Gershon and reported by Martin[16]. The analeptic effect of succinate in man has been found to be directly related to the depth of narcosis and the dose required is entirely dependent on the individual and the depth of depression. The succinate may be given with complete safety in the treatment of supposed or assumed morphine or barbiturate poisoning or a combination of the two.

## Discussion

Numerous drugs of differing chemical structure can alleviate the narcotic action of morphine in dogs[7,10–12]. The same drugs have a less positive effect on narcosis and respiratory effect in man[1]. Both in man and animals these drugs do not affect the analgesia, as do the specific morphine antagonists like nalorphine. In addition the members of the miscellaneous group have very little effect themselves on the animals in doses which bring about the antagonism.

Without exception the antihistamine drugs tested restore consciousness to dogs given morphine; they effect a slight improvement in respiration, but do not restore normal tone to the limb muscles. In this latter respect they differ from amiphenazole and tetrahydroaminacrin[10]. The administration of histamine before morphine results in an increase in the rapidity of the onset of narcosis and the action of an antihistaminase is consistent with this result as is actions of the antihistamine drugs. Paradoxically histamine injected during narcosis transiently improves the level of consciousness. It would thus appear that at least part of the pharmacology of morphine is mediated by the release of histamine. It should be pointed out however, that the improvement brought about in a morphine-treated dog by the antihistamine drugs is brief and requires large doses. It is possible that the beneficial effect is not due to the antihistaminic activity but to an additional central action.

In many of the animals gross effects of histamine-release were seen, such as redness and oedema of the eyelids, and also of the areas above the eyes; there was also general swelling of a limb around the site of injection. In man, an extensive wheal is often produced around the site of intravenous injection, and a red streaking extending along the draining vein. The production of an urticarial response by morphine when applied to an area of scarification of the skin was described by Sollman and Pilcher[13]. Nasmyth and Stewart[3] found that morphine and codeine elicit a triple response. Similar phenomena can be produced in the human skin with diamorphine, papaverine and pethidine injected intradermally, and these responses are reduced by antihistamines. In cats intravenous morphine produces a sudden fall in blood pressure of 30 minutes duration. This response is similar to that obtained with the injection of histamine. Nasmyth and Stewart[3] also showed that opium alkaloids produced a release of histamine from a rat diaphragm preparation. Feldberg and Paton[2] in experiments on cats confirmed the above findings. They found that morphine and codeine given intravenously caused a fall in arterial blood pressure, and once fallen the blood pressure stays low. This prolonged action is unlike any of the other histamine liberators.

The release of histamine is probably the cause of the idiosyncracy to morphine and pethidine in some people as well as the hypersensitivity observed in those with bronchial asthma. The clinical aspects of histamine release are discussed in another paper in which the anti-emetic effect of cyclizine on morphine-induced emesis is well demonstrated[1].

The compounds investigated did not grossly affect the analgesic state and it seems probable that the pain aleviation mechanism differs from the histamine releasing syndrome.

The analeptic action of succinic acid merits discussion. Succinate is outstanding amongst the other intermediates of the tricarboxylic acid cycle, because unlike others, its dehydrogenation to fumarate proceeds directly to the cytochrome system over an intermediate barbiturate-sensitive flavine system[17]. It is therefore not surprising that it is equally readily oxidised in the presence or absence of barbiturate. It has been shown that certain drugs other than the barbiturates such as chloretone, scopolamine

and diphenyloxazolidinedione are also specific depressants of oxidation of glucose and pyruvate at levels of concentration that do not effect succinate. Quastel and Wheatley[18] also demonstrated that the addition of 0·12 per cent morphine caused an inhibition of oxygen consumption by cerebral tissues. Seevers and Shideman[19] reported the blockade by morphine of the activity of lactic, citric and glucose dehydrogenases, and that succinic and ethanol dehydrogenase were not affected. It has been shown that succinate alone remains oxidisable both in anaesthesia and oxygen poisoning, and thus it may be that this simple aliphatic drug might be a valuable physiological antidote in various conditions of central nervous system depression.

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