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THE ACTION OF ANALGESICS AND NALORPHINE ON THE COUGH REFLEX

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Although the effects of various morphine-like analgesics on pain, respiration, body temperature, and gastrointestinal propulsion have been extensively examined and compared in several animal species, the antitussive action of these compounds has received relatively little attention. We therefore compared analgesics of several distinct chemical types, and also pholcodine and narcotine. For most of these comparisons we used the method of Domenjoz (1952) whereby respiratory efforts simulating those of coughs are elicited in anaesthetized cats by electrical stimulation of the superior laryngeal nerve. In addition, we examined the actions of codeine and of nalorphine on coughs due to various stimuli in cats, dogs, and guinea-pigs.

METHODS

Cats, dogs, and guinea-pigs were lightly anaesthetized with pentobarbitone sodium—30 to 40 mg./kg. i.p. and more as required i.v.—deep anaesthesia being avoided as this inhibited the cough reflex. In some experiments guinea-pigs were decerebrated under short ether anaesthesia.

Electrical stimulation of the central end of the cut superior laryngeal nerve drawn into a fluid electrode of the type described by Porter and Allamon (1936) was used to elicit respiratory efforts in cats. The stimulus consisted of pulses having a wave form approximating to that of capacitor discharge delivered at the rate of 6 to 10/sec. for periods of 3, 5, or 10 sec. from a blocking oscillator with constant voltage output (Dickinson, 1950). The pulse potential (usually 1–5 volts) was adjusted so as to cause a series of inspiratory gasps. These were recorded by a lightly sprung lever attached by a thread to the skin just below the sternum. An example of the type of tracing obtained is shown in Fig. 1. This method of stimulation was also tried in dogs, but, like Domenjoz (1952), we failed to produce a similar effect in this species.

A simple mechanical method—passing a thin polythene tube in and out of the trachea two or three times—was used to elicit short bursts of coughing in anaesthetized cats, dogs, and guinea-pigs.

Chemical stimulation was also used in unconscious animals. In cats and guinea-pigs 0.05 ml. (or less if effective) of SO_2 at atmospheric pressure, withdrawn from an SO_2 syphon in a syringe, was introduced into the tracheal cannula. This regularly caused coughing when, as in our experiments, an interval of about 8 min. was allowed between tests. In dogs these small volumes of undiluted SO_2 did not always induce coughing, and after larger amounts the animals frequently became refractory. More consistent responses were obtained by making the animal breathe an approximately 1:100 dilution of SO_2 in air from a bag until coughing occurred or for a maximum of 3 breaths, but some animals became refractory, and we have therefore reported only those experiments in which the SO_2 effect subsequently returned after suppression by an analgesic. Like the responses to electrical stimulation, those due to mechanical and chemical irritation were recorded from the abdomen except in three experiments in which a body plethysmograph, of the type described by Dawes, Mott, and Widdicombe (1951), was used to examine the nature of the responses more closely. These were found after each of the three types of stimulation to consist of one or more deep inspirations each followed by rapid forced expiration. The first inspiration was usually, but not invariably, preceded by a rapid expiratory movement.

Analgesics and other drugs were given intravenously in all experiments. In most experiments, including all of those in Table I, increasing doses in the series 0.01, 0.03, 0.1, 0.3, 1.0, 3.0, 10, and 30 mg./kg. were given. Sufficient time for recovery, or 10 min. after ineffective amounts, was generally allowed between doses.

Development of acute tolerance to the respiratory depressant action of codeine was investigated in cats anaesthetized with pentobarbitone sodium by comparing the action on respiratory minute-volume (recorded as by Gaddum, 1941) of a single large dose of codeine with that of a series of increasing doses. The series was that used by May and Widdicombe (1954): 0.5 + 0.5 + 1.0 + 2.0 + 4.0 + 8.0 + 16 mg./kg. given at intervals of approximately 5 min. The experiment was of cross-over design; on the first day the series of doses was given to one cat and the single

large dose to the other cat, the cross-over test being carried out 3 days later.

The doses of the compounds are those of the salts referred to in Table I. Nalorphine was used as hydrochloride.

RESULTS

Antitussive Action

Cats.—The respiratory gasps caused by stimulating the superior laryngeal nerve were inhibited by each of the analgesics to an extent which varied with the dose. Table I shows the number of cats in a group, in which the inhibition was complete for at least 5 min. after progressively increasing doses of the analgesics. The relative potencies of the analgesics cannot be defined except at arbitrary levels, as the dose-probit response relationship is not the same for each compound. Thus, for example, the probit response increases more sharply with the dose of methadone than with the dose of morphine. Comparison of the ED50 values indicates that methadone is the most powerful suppressant of the reflex in these animals, its activity being perhaps slightly greater than that of piperidylamidone, about eight times that of morphine, twenty times that of pethidine, and about eighty times that of codeine.

TABLE I

THE NUMBER OF CATS IN WHICH THERE WAS COMPLETE SUPPRESSION, BY VARIOUS INTRAVENOUS DOSES OF ANALGESICS, OF COUGHS PRODUCED BY ELECTRICAL STIMULATION OF THE SUPERIOR LARYNGEAL NERVE

	No. of Cats Tested	Dose (mg./kg.) 0·03	0·1	0·3	1·0	3·0	10·0	30	Approx. ED50 (mg./kg.)
Morphine sulphate	7	0/3	1/7	3/7	5/7	7/7			0·4
Codeine (base) ..	6		0/6	0/6	1/6	2/6	6/6		4
Pethidine hydrochloride . ..	4		0/4	1/4	2/4	4/4			1
Methadone hydrochloride.. ..	6	1/4	6/6						0·05
Piperidylamidone* hydrochloride ..	4		1/4	2/4	4/4				0·1
Thiambutene† hydrochloride ..	2	0/2	0/2	2/2					0·2
Pholcodine (base)	4				0/4	1/4	3/4	3/4 4/4	2
Narcotine hydrochloride.. ..	2		0/2	0/2	0/2	0/2	1/2		30

* 6-Piperidino-4: 4-diphenyl-3-heptanone hydrochloride (Ofner, Walton, Green, and White, 1950).

† 3-Diethylamino-1: 1-di-2′-thienylbut-1-ene hydrochloride (Green, 1953).

The duration of the suppression varied between compounds and with the dose administered. The effects of 3 mg./kg. morphine, 0.1 mg./kg. methadone, 3 mg./kg. pethidine, 0.3 mg./kg. piperidylamidone, and 30 mg./kg. pholcodine lasted for at least 2 hr., that of 3 mg./kg. codeine for about 1 hr., and those of 0.3 and 1 mg./kg. thiambutene for 15 min. and some 2 hr. respectively.

The effectiveness of codeine or narcotine was shown not to depend on the type of stimulus initiating the cough reflex. The effects of electrical, mechanical, or chemical stimuli were reduced equally by 0.3–1 mg./kg. and abolished by 3–10 mg./kg. codeine in each of three cats, and were unaffected by 10 mg./kg. and nearly abolished by 30 mg./kg. narcotine in one cat.

Dogs.—Coughs elicited by mechanical stimulation were abolished by 1 mg./kg. codeine in two of five dogs, and by 3 mg./kg. in each of five dogs. Coughs caused by SO_2 were abolished by 1 mg./kg. codeine in each of two dogs.

Guinea-pigs.—The dose of codeine required to suppress respiratory efforts due to either mechanical stimulation or SO_2 was approximately 10 mg./kg. in one decerebrate and two anaesthetized guinea-pigs.

Narcotine was ineffective at 10 mg./kg., and even 30 mg./kg. abolished the effects of mechanical and chemical stimuli in only one of two guinea-pigs.

Antagonism by Nalorphine

Nalorphine, in doses varying between 3 and 30 mg./kg., did not abolish the cough reflex induced by electrical, mechanical, or chemical stimulation in three anaesthetized cats; it did not abolish the reflex to mechanical stimulation in five unanaesthetized dogs; and it was likewise ineffective against mechanical or chemical stimulation in four anaesthetized and two decerebrate guinea-pigs.

Nalorphine rapidly abolished the antitussive action of morphine-like analgesics. The return of electrically induced respiratory efforts which had been suppressed by morphine, after the intravenous injection of nalorphine, is illustrated by Fig. 1. The effective dose of nalorphine varied with the dose and potency of the analgesic, and was of a similar order of magnitude to that antagonizing other morphine-like effects, (e.g., respiratory depression in these experiments). The following results obtained from a small number of tests provide a very rough estimate of the effectiveness of nalorphine against various doses of the analgesics. A dose of 0.1 mg./kg. nalorphine abolished the action of 0.3–1 mg./kg. morphine, of 0.1 mg./kg. methadone, and of 0.3 mg./kg. piperidylamidone; 0.3 mg./kg. nalorphine abolished the action of 1–3 mg./kg. morphine, of 1 mg./kg. thiambutene, and of 3 mg./kg. codeine; 1 mg./kg. nalorphine abolished the action of 0.3 mg./kg. methadone and of 3 mg./kg. pethidine; and 3 mg./kg. nalorphine abolished the action of 1 mg./kg.

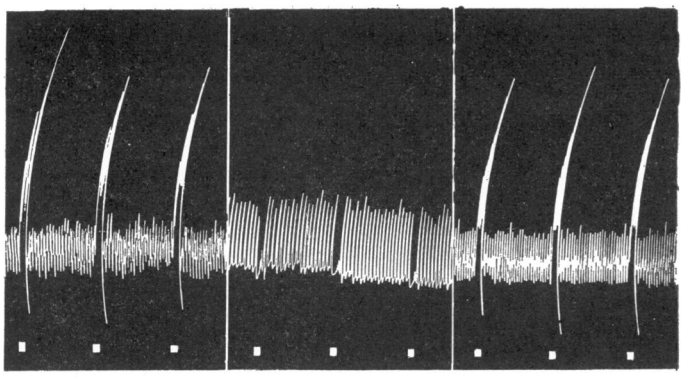

FIG. 1.—Record of coughs caused by electrical stimulation of the superior laryngeal nerve in an anaesthetized cat. Stimulus: 6 cycles/sec. for 10 sec. every 2 min. A, Initial. B, After 1 mg./kg. morphine sulphate i.v. C, After 0.3 mg./kg. nalorphine hydrochloride i.v. given 10 min. after the morphine. Inspiration is represented by an upward movement.

methadone and of 10 mg./kg. codeine. Nalorphine was equally effective in reducing or abolishing the suppressant action of codeine on coughs due to electrical, mechanical, or chemical stimulation in each of three cats. *N*-propylnormorphine (10 mg./kg.; lower doses were not tried) also eliminated the antitussive action of codeine (20 mg./kg.) in a cat. In an anaesthetized dog the suppressant action of 10 mg./kg. codeine on mechanically induced coughs was abolished by 1 mg./kg. nalorphine. Likewise in one decerebrate and two anaesthetized guinea-pigs, 1–3 mg./kg. nalorphine prevented or abolished the action of 10 mg./kg. codeine on mechanically or chemically induced coughs.

Some observations made on a dog with a natural cough, readily initiated by exposure to cold, are of interest. The cough was completely suppressed by 3 mg./kg. codeine i.v., but returned soon after giving 1 mg./kg. nalorphine i.v. Nalorphine, 1 mg./kg., alone failed to reduce the cough when tested on the following day; 3 mg./kg. did not abolish the cough but may have been responsible for a slight reduction in its severity. In another dog, natural coughing suppressed by methadone was restored by *N*-propylnormorphine.

In anaesthetized cats the antitussive action of 3 mg./kg. pholcodine or 30 mg./kg. narcotine was not antagonized by 10 mg./kg. nalorphine.

Effects on Breathing

Morphine, codeine, methadone, piperidylamidone, and thiambutene frequently reduced the rate of breathing in anaesthetized cats at doses the same as, or slightly above, those suppressing the respiratory response to stimulating the superior laryngeal nerve (Table II). With doses which just suppressed this response, the percentage reduction of respiratory frequency was usually small, e.g., a mean reduction of 21% (S.D. ±9) with 0.1 mg./kg. methadone which abolished the cough in each of six cats, but in two cats codeine caused a great, though temporary, respiratory depression, and in two cats morphine caused persistent reduction (50 and 90%). Pethidine suppressed the cough without depressing respiration. Pholcodine depressed the respiration in one cat, and increased the frequency in others. Narcotine (10–30 mg./kg.) caused brief apnoea followed by an increase in frequency of breathing.

Antitussive doses of codeine (1–3 mg./kg.) had no effect on respiration in three anaesthetized dogs, and slightly increased the rate in two others; 10 mg./kg. codeine had no effect in one guinea-pig and reduced the frequency by about 30% in another.

Codeine caused rapid breathing in one of six cats in our experiments, and three of six cats in those of May and Widdicombe (1954). Further investigation showed that the action of codeine depended on the dose schedule. Thus, in a cross-over test using two cats, single large doses (8 mg./kg.) greatly decreased the respiratory minute-volume, whereas the same amount or more in divided doses produced rapid shallow breathing (Fig. 2). In other tests, although first doses of 1 or 3 mg./kg. codeine caused marked respiratory depression, later doses of 3 to 10 mg./kg. caused less depression. The development of tolerance to the depressant action of codeine may have been more marked in the experiments of May and Widdicombe (1954)—who gave the series of doses in Fig. 2 at 10-min. intervals—than in ours with larger dose steps and a greater interval between

TABLE II

THE NUMBER OF CATS IN WHICH THE FREQUENCY OF BREATHING WAS REDUCED BY AT LEAST 30%, 2 MIN. AFTER VARIOUS INTRAVENOUS DOSES OF ANALGESICS

	No. of Cats Tested	Dose (mg./kg.)				
		0·1	0·3	1·0	3·0	10·0
Morphine	7	0/7	0/7	2/6	2/2	
Codeine	6	0/6	0/6	1/6	3/6	3/5
Pethidine	4	0/4	0/4	0/4	0/2	0/1
Methadone	6	1/6	1/2			
Piperidylamidone ..	4	0/4	1/2			
Thiambutene	2	0/2	1/2	1/2		
Pholcodine	4		0/4	1/4	1/4	0/1

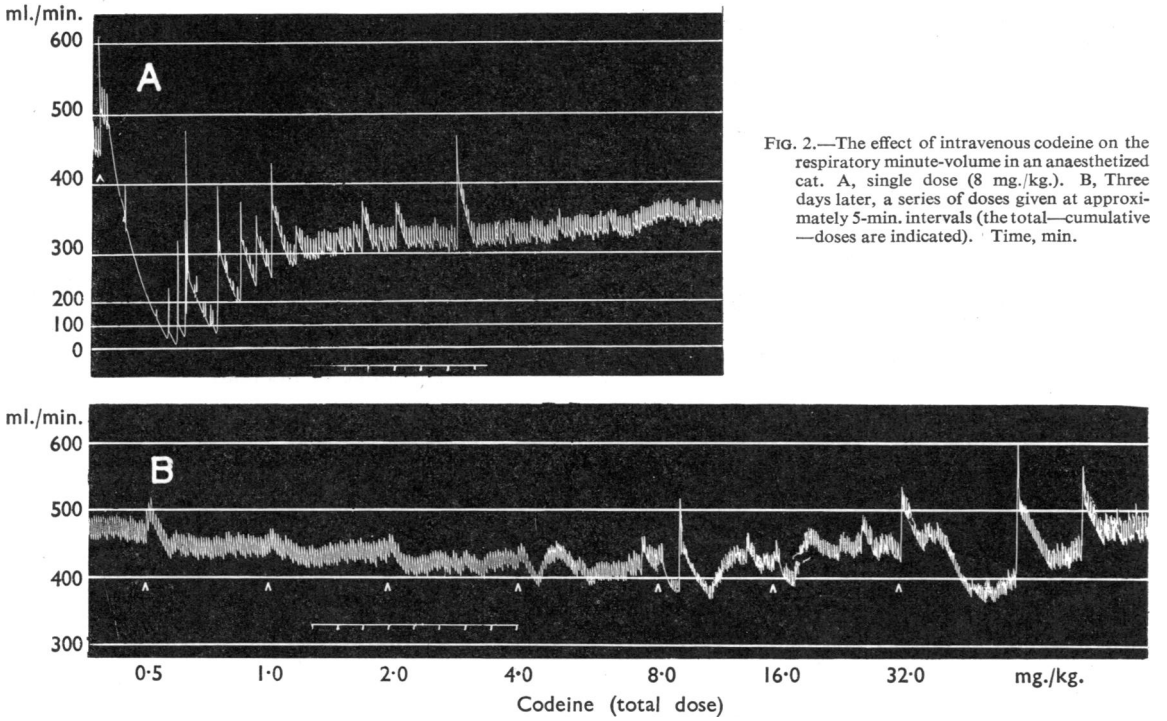

FIG. 2.—The effect of intravenous codeine on the respiratory minute-volume in an anaesthetized cat. A, single dose (8 mg./kg.). B, Three days later, a series of doses given at approximately 5-min. intervals (the total—cumulative—doses are indicated). Time, min.

doses. Respiratory depression was predominant in the experiments of Toner and Macko (1952), who gave single doses of 1 mg./kg. There was no indication in our experiments of acute tolerance developing to the antitussive action of codeine or other analgesics.

The dose of nalorphine that eliminated the respiratory depressant action of the analgesics was usually about half that which eliminated the antitussive action. This is in keeping with the observation that analgesics usually suppressed the cough reflex before they depressed the respiration.

DISCUSSION

In all our experiments the respiratory gasps, caused by electrical stimulation of the central end of the superior laryngeal nerve in the cat, closely resembled those caused by mechanical or chemical irritation of the bronchial system, and they responded in the same way to analgesics, to nalorphine and to narcotine. This indicates that the main effect observed during stimulation of this mixed nerve arises from excitation of afferent fibres which are the same as, or similar to, those excited by mechanical or chemical stimuli. This effect may therefore justifiably be used for the investigation of antitussive action.

The doses of the various compounds which suppressed the response to electrical stimulation of the superior laryngeal nerve in anaesthetized cats (Table I) are—allowing for minor variations in technique, and the considerable variations in the sensitivity of different cats to morphine and codeine—in keeping with the results obtained for morphine, codeine, and methadone by Domenjoz (1952) and for codeine by Toner and Macko (1952), who used similar methods. They are also of the same order of magnitude as the doses of morphine, codeine, and pholcodine which May and Widdicombe (1954) found to suppress coughs—referred to, in their paper, as inspiratory efforts—caused by mechanical or chemical irritation in anaesthetized cats. Kasé (1952, 1955) found that, for suppression of coughs caused by intense mechanical stimulation of the trachea in conscious dogs, the minimum effective intravenous doses were approximately as follows: morphine, 0.5 mg./kg.; codeine, 3 mg./kg.; pethidine, 3 mg./kg.; methadone, 0.5 mg./kg.; and narcotine, 10 mg./kg. With the exception of the methadone dose, which is somewhat greater, these amounts are similar to those found by various methods to be effective in cats. Further, we have found, using mechanical or chemical irritation, that the effective dose of codeine is similar in cats, dogs and guinea-pigs, and that the effective dose of narcotine was similar in cats and guinea-pigs. Therefore in these experiments the activities of compounds in suppressing

the cough reflex have not varied to any great extent either with the stimulus used for initiating the reflex or with the species. Further, effective doses in lightly anaesthetized animals have been similar to those in conscious animals. The agreement between the results obtained in such experiments is, however, not complete, for in a preliminary report Konzett and Rothlin (1954) state that 1 mg./kg. narcotine suppressed coughs caused by mechanical stimulation in anaesthetized cats, whereas we and Kasé (1955) find the minimal effective dose of this drug to be at least 10 mg./kg.

Nalorphine itself did not abolish the cough reflex, but abolished the action of morphine-like analgesics in all the experiments described. *N*-propylnormorphine, which shares other actions of nalorphine (Green, Ruffell, and Walton, 1954), showed the same antagonism to the suppressant action of codeine. The effective doses of the analgesics and nalorphine in these experiments are of the same order of magnitude as those known to produce effects on pain threshold, respiration, body temperature, and gastrointestinal propulsion. It is therefore concluded that similar drug receptor sites and mechanisms may be involved in the causation of these effects.

In contrast with the above findings, Winter and Flataker (1954) report that the frequency of coughing in conscious dogs and guinea-pigs forced to breathe mild irritants is reduced by low subcutaneous and oral doses of nalorphine, narcotine, or codeine, and that the effect of nalorphine is synergistic with that of codeine and narcotine. The effective doses determined by Winter and Flataker (1954, 1955) are, as we and others have shown, much less than those needed to depress or abolish the cough reflex or other nocioceptive reflexes. The effects they observed are therefore probably caused by some other mechanism, such as a decreased perception of the mild irritant or a depressed psychological reaction to it, for coughing during exposure to mild irritants is to some extent voluntary. Further, the reduction by small doses of narcotine of the frequency of coughing during anaphylactic shock in guinea-pigs (Winter and Flataker, 1955) cannot easily be explained by suppression of the cough reflex. The question arises: which type of experimental method is the most suitable for selecting new antitussive drugs for clinical investigation ? That the methods such as we and others have used in anaesthetized animals, and that which Kasé (1952, 1955) has used in conscious dogs, are perhaps to be preferred to those of Winter and Flataker (1954) is indicated by the controlled experiments of Gravenstein, Devloo, and Beecher (1954), which show that in man only relatively high doses of analgesics suppress pathological or chemically induced cough, and that moderate doses of narcotine and nalorphine are not cough suppressants.

The cough suppressant action of pholcodine has been distinguished from that of morphine-like analgesics by its relatively greater effect on " expiratory " than on " inspiratory " efforts (May and Widdicombe, 1954). The failure of nalorphine to antagonize its effects is further evidence of a different mode of action. By the same means, the action of narcotine has been distinguished from that of morphine-like compounds.

Summary

1. The antitussive actions of intravenous morphine, codeine, pethidine, methadone, piperidylamidone, thiambutene, pholcodine, and narcotine have been compared on coughs caused by electrical stimulation of the superior laryngeal nerve in anaesthetized cats. Codeine was also tested on mechanically and chemically induced coughs in anaesthetized cats, guinea-pigs, and dogs, and on a natural cough in a dog. Nalorphine was tested alone and in combination with the morphine-like drugs.

2. Methadone was the most powerful suppressant of coughs caused by the electrical stimulus in cats ; its activity was slightly greater than that of piperidylamidone, about eight times that of morphine, twenty times that of pethidine, and eighty times that of codeine in cats. Pholcodine was slightly more active than codeine. Narcotine was relatively ineffective.

3. Suppression of the cough reflex by codeine and narcotine did not seem to be dependent on the type of stimulus ; nor did cats, dogs, and guinea-pigs show great species variation in sensitivity to these drugs.

4. The suppressant doses of the analgesics were of the same order of magnitude as those known to cause other morphine-like effects. Relative to its antitussive action, morphine had the greatest, and pethidine the least, effect on breathing in the cat.

5. Nalorphine itself had no effect on the cough reflex, but readily abolished the suppressant action of morphine-like analgesics ; similarly *N*-propylnormorphine eliminated the effect of codeine. The actions of pholcodine and narcotine were not antagonized by nalorphine.

6. The results obtained by these methods are compared with those from other experimental procedures.

7. Acute tolerance rapidly developed to the respiratory depressant action of codeine in the cat.

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