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QUANTITATIVE STUDIES OF THE ANTAGONISM BY NALORPHINE OF SOME OF THE ACTIONS OF MORPHINE-LIKE ANALGESIC DRUGS

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A quantitative investigation has been made of the antagonism by nalorphine of the analgesia and lenticular opacity produced in mice by a number of compounds. ED50 values have been obtained for each drug in the absence and in the presence of increasing doses of nalorphine, and from these, appropriate dose-ratios have been calculated. It has been possible to derive the equivalent of a pA_2 value for each drug with nalorphine and, since these are almost identical, it may be concluded that all the drugs combine with similar receptors. Nalorphine antagonizes both actions by competing for the receptors. It was not possible to antagonize quantitatively the analgesic action of pethidine with nalorphine, although the lenticular effect could be abolished. The effect of nalorphine on the change in skin temperature in mice induced by some of the analgesic drugs was also investigated.

It has been suggested that nalorphine antagonizes the analgesic action of morphine and that of many related compounds by competing with them for an essential receptor site. (Seibert & Huggins, 1953 ; Landmesser, Cobb & Converse, 1953 ; Lasagna, 1954.) However, the evidence for the competitive nature of the antagonism is only indirect and has not been clearly demonstrated by accepted pharmacological techniques. It has largely been inferred from the rapidity with which the effects of analgesic drugs are antagonized by nalorphine and from a similarity of the chemical configurations of the active compounds and the antagonists (Fromherz & Pellmont, 1952 ; Green, Ruffell & Walton, 1954 ; Beckett & Casy, 1954 ; Beckett, Casy & Harper, 1956).

In order to demonstrate that nalorphine antagonizes a given action of morphine by competition for the receptors, it is necessary to measure an effect produced by the drug alone, and then in the presence of a series of doses of nalorphine. From these measurements it should be possible to derive a pA_2 value for a given action of morphine (Schild, 1947). The significance of the pA_x determination lies in the identification of receptors on which drugs are presumed to act. Thus if several drugs act on the same receptors they can be expected to give the same pA_x value with nalorphine. Furthermore, if nalorphine produces the same pA_x in different preparations it can be assumed that the receptors with which it reacts are similar (Schild, 1957).

In an earlier paper it had been shown that morphine-like analgesic drugs can produce a reversible lenticular opacity in rodents, and that this effect can be antagonized by nalorphine (Weinstock, Stewart & Butterworth, 1958). From the results of a comparative study of the analgesia and lenticular opacity activities of a large number of compounds, including isomeric pairs, it was suggested that the receptors involved in the mediation of the two effects were similar (Weinstock, 1961).

An investigation was therefore made of both the analgesic activity and that on the lens of mice of several different drugs in the presence of increasing doses of nalorphine. It was hoped that competitive antagonism could be demonstrated between nalorphine and the drugs for each action, and that more information could be derived concerning the nature of the receptors involved.

METHODS

Male and female mice, of a Smith, Kline & French (Albino) strain, and weighing 20 to 24 g, were used.

Analgesic activity

The modification of the hot-plate method of Eddy & Leimbach (1953), described by Janssen & Jageneau (1957) and Weinstock (1961), was used for measuring analgesic activity.

The reaction times of mice, measured to 0.2 sec, were determined twice before and 15, 30, 45, 60, 90 and 120 min after subcutaneous injection of the drug. All animals whose mean initial reaction time exceeded 10 sec or for which the two readings differed by more than 100%, were discarded. A response was considered positive if the reading after injection was greater than 30 sec or if it exceeded the initial mean reading by a factor of 3 or more. The number of such positive responses was noted at each of the various times. The largest number of such positive responses occurring for each dose at a given time was converted to a percentage and used in the plotting of the dose/response curves.

Opacity-producing activity

Mice were examined at 15, 30, 45, 60, 75, 90 and 120 min after injection of the drug, and the number of opacities which occurred at the various times was recorded. The largest number of opacities occurring with each dose was converted to a percentage and used in the plotting of the dose/response curves.

For both the analgesia and the lenticular opacity experiments, all drugs were administered as aqueous solutions of their salts in a constant volume of 1.0 ml./100 g. Nalorphine was injected subcutaneously followed immediately by the analgesic drug, given by the same route.

Dose/response lines for opacity and analgesia were constructed for each drug given alone, and together with various doses of nalorphine (see Fig. 1). At least three doses of each drug were given alone, and with nalorphine. A minimum of twenty mice was used for each dose. ED50 values were determined from the dose/response lines, and their fiducial limits of error were computed by the method of Litchfield & Wilcoxon (1949). Dose-ratios were calculated from the ED50 values for each drug.

Measurement of skin temperature and its response to drugs

Groups of five mice were cooled to various temperatures by placing them in metal containers inside a box packed with ice. The skin temperatures were then measured on a shaved area of the back by means of a thermometer operating on the thermocouple principle, which was calibrated to read directly in degrees centigrade. The reaction-times of the mice on the hot-plate were determined immediately afterwards.

Groups of five to ten mice were injected subcutaneously with the analgesic drug alone, or together with nalorphine. The skin temperatures were measured immediately before the injection, and 15 to 30 min afterwards. A group of mice given 0.9% saline served as controls, so that allowance could be made for any changes which occurred in skin temperature as a result of possible fluctuations in environmental conditions.

Drugs

These were morphine sulphate, methadone hydrochloride, pethidine hydrochloride, diamorphine hydrochloride, levorphanol hydrogen tartrate (Dromoran), dextromoramide bitartrate (Palfium), nalorphine hydrobromide (Lethidrone), and a very potent new analgesic drug, 3-*O*-acetyl-6,14-*endo*-etheno-5,7,8,8-tetrahydro-7α-(2-hydroxypent-2-yl)oripavine hydrobromide (M183; Bentley & Hardy, 1963).

RESULTS

The typical dose/response curves obtained for the opacity-producing activity of methadone are shown in Fig. 1. Similar series of curves were constructed for each

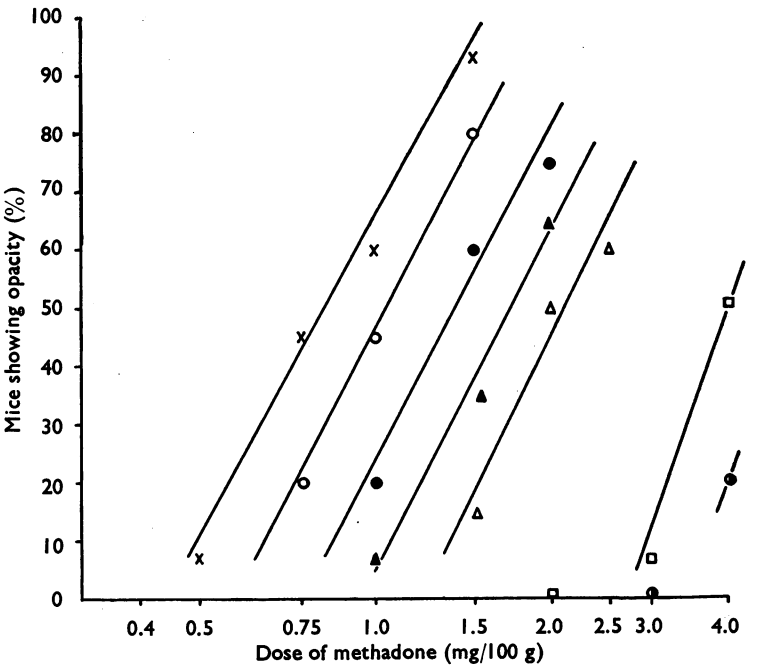

Fig. 1. Dose/response lines for opacity produced by methadone alone and in the presence of nalorphine. Abscissa (log scale): dose of methadone in mg/100 g of body weight; ordinate: number of mice showing opacity at time of maximum activity of drug, expressed as a percentage. ×—×, methadone alone; ○ — ○, methadone with nalorphine, 0.01 mg/100 g; ● — ●, with nalorphine, 0.025 mg/100 g; ▲ — ▲, with nalorphine, 0.05 mg/100 g; △ — △, with nalorphine, 0.075 mg/100 g; □ — □, with nalorphine, 0.10 mg/100 g; and ◑—◑, with nalorphine, 0.20 mg/100 g.

of the other analgesic drugs. From these curves the ED50 values were calculated for each drug alone, and in the presence of increasing doses of nalorphine. These values are shown in Table 1 together with the dose-ratios.

TABLE 1

DOSE-RATIOS FOR THE LENTICULAR OPACITY ACTIVITIES OF DRUGS IN THE PRESENCE OF NALORPHINE TO THOSE IN THEIR ABSENCE

All doses are in mg of the salt/100 g of body weight

Drug	Dose of nalorphine (mg/100 g)	ED50 for opacity	Fiducial limits (%, P=0·95)	Dose ratio (x)
Morphine	0	4·8	84–120	—
	0·025	7·0	71–141	1·46
	0·05	9·9	70–142	2·06
	0·1	15·8	68–147	3·28
Methadone	0	0·78	90–111	—
	0·01	1·06	90–111	1·36
	0·025	1·28	86–117	1·64
	0·05	1·68	87–115	2·15
	0·075	2·10	86–117	2·70
Diamorphine	0	1·06	74–136	—
	0·01	1·50	68–143	1·44
	0·025	2·25	72–139	2·13
	0·05	3·70	67–145	3·49
Dextromoramide	0	0·235	72–140	—
	0·01	0·330	70–142	1·41
	0·025	0·490	73–138	2·08
	0·05	0·710	72–140	3·10
Levorphanol	0	1·18	82–122	—
	0·01	1·66	76–133	1·41
	0·025	2·36	67–148	2·00
	0·05	3·35	75–134	2·85
Pethidine	0	4·10	88–114	—
	0·01	4·65	72–127	1·14
	0·025	6·1	82–120	1·49
	0·05	7·4	82–120	1·81
	0·10	11·5	72–127	2·82
M183	0	0·0019	79–127	—
	0·01	0·0026	88–114	1·34
	0·025	0·0040	89–113	2·08
	0·05	0·0055	88–114	2·90

Arunlakshana & Schild (1959) have shown that when log (x-1), where x is the dose-ratio, is plotted against the negative log of the molar concentration of antagonist (B), a linear relationship results if the agonist and antagonist compete for the same receptors. All the experiments that they have described were carried out with isolated organ preparations, where the concentration of the antagonist may be readily controlled. In our experiments, in which whole animals were used, the concentration of nalorphine at the site of action was unknown, so that we had to plot, instead, the negative log of the molar dose of nalorphine injected into the animals on a weight basis. We have called this value N. It was assumed to be proportional to the concentration of nalorphine at the site of action. Fig. 2 shows the results obtained when log (x-1) is plotted against N, with methadone as the active drug. A linear relationship resulted, except when very high doses of methadone, in the lethal range, were used. This allows derivation of the equivalent of a pA_2 value from the point of intersection of the line and the abscissa. Results from experiments with six other analgesic drugs were also fitted by straight lines (Fig. 3). The "pA_2" values were computed for each drug and are shown in Table 2.

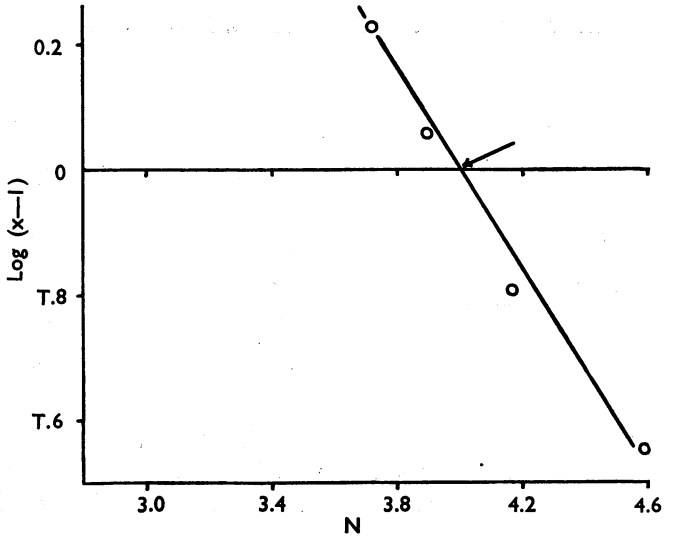

Fig. 2. Relationship between dose-ratios for opacity test with methadone and corresponding doses of nalorphine from which they are derived. Abscissa: N, the negative logarithm of the molar dose of nalorphine injected per 100 g of body weight. Ordinate: log (x—1), where x is dose-ratio shown in Table 1. The arrow indicates the "pA_2" value.

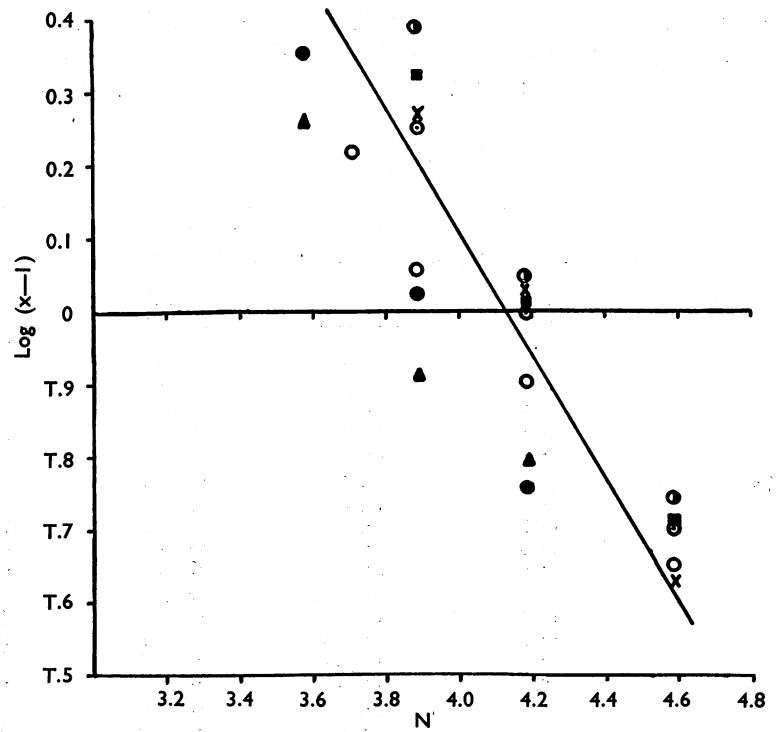

Fig. 3. Relationship between dose-ratios and doses of nalorphine for opacity produced by several analgesic drugs. Abscissa: N, the negative logarithm of the molar dose of nalorphine injected per 100 g of body weight; ordinate: log (x—1) where x is dose-ratio shown in Table 1. ●—●, morphine; ⊙—⊙, levorphanol; ◑—◑, diamorphine; ■—■, dextromoramide; ▲—▲, pethidine; ○—○, methadone; and ×—×, M183.

TABLE 2

"pA_2" VALUES FOR ANALGESIC DRUGS WITH NALORPHINE IN OPACITY TEST

Drug	"pA_2"	Time of maximum activity of drug (min)
Pethidine	3·90	30
M183	4·20	30
Dextromoramide	4·22	30
Diacetylmorphine	4·25	30
Levorphanol	4·19	45
Methadone	3·99	45
Morphine	3·92	60–75

It was not possible to obtain further data using higher concentrations of nalorphine because the doses of analgesic drugs that would have been required came in most cases into the lethal range, so that accurate dose/response lines could no longer be obtained.

Similar series of dose/response curves were constructed for the analgesic activity of morphine, methadone, pethidine and M183; the ED50s were determined and the dose-ratios calculated for each drug together with various doses of nalorphine. The ED50 values with their 95% fiducial limits of error and the dose-ratios for four analgesic drugs are shown in Table 3. Fig. 4 shows the results obtained by plotting log (x-1) against the negative log of the molar dose of nalorphine (N).

TABLE 3

DOSE-RATIOS FOR THE ANALGESIC ACTIVITY OF DRUGS IN THE PRESENCE OF NALORPHINE TO THOSE IN THEIR ABSENCE

All doses are in mg of the salt/100 g of body weight

Drug	Dose of nalorphine (mg/100 g)	ED50 for analgesia	Fiducial limits (%, P=0·95)	Dose ratio (x)
Morphine	0	0·94	71–135	—
	0·025	1·65	77–132	1·76
	0·035	2·52	70–137	2·70
	0·05	3·60	73–137	3·83
	0·10	4·90	75–133	5·22
Methadone	0	0·46	85–119	—
	0·025	0·89	72–138	1·94
	0·035	1·31	76–133	2·85
	0·05	1·85	68–148	4·02
	0·10	2·10	82–122	4·57
M183	0	0·00077	84–119	—
	0·01	0·00115	64–156	1·50
	0·025	0·00170	78–127	2·18
	0·05	0·0028	85–118	3·64
	0·10	0·0037	78–127	4·80
Pethidine	0	2·05	84–119	—
	0·025	3·15	84–119	1·54
	0·035	4·25	84–120	2·04
	0·05	4·00	84–120	1·96
	0·10	4·10	77–130	2·00
	0·20	3·15	81–123	1·54
	0·40	3·3	81–124	1·61
	0·80	3·3	82–122	1·61

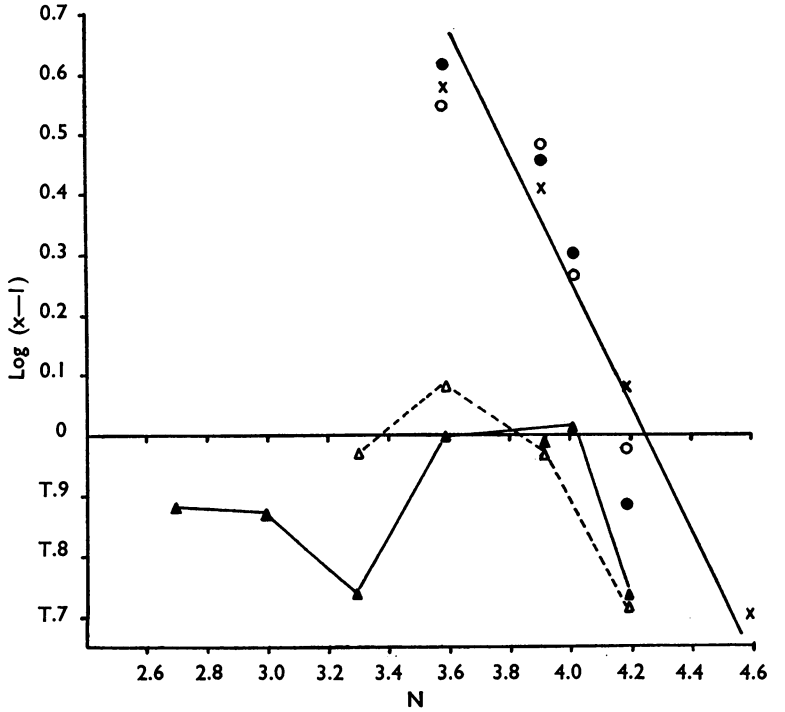

Fig. 4. Relationship between dose-ratios and doses of nalorphine for analgesic activity of several compounds. Abscissa: N, the negative logarithm of the molar dose of nalorphine injected per 100 g of body weight; ordinate: log (x−1), where x is the dose-ratio shown in Table 3. ●—●, morphine; ○—○, methadone; ×—×, M183; ▲—▲, pethidine; and △—△, pethidine corrected for the effect on body temperature.

Although morphine, methadone and M183 again gave linear relationships, as in the opacity experiment, the analgesia induced by pethidine could be only partially antagonized, even when the amount of nalorphine was increased tenfold. The "pA_2" values for the analgesic activities of morphine, methadone and M183 are shown in Table 4.

TABLE 4

"pA_2" VALUES FOR ANALGESIC DRUGS WITH NALORPHINE FOR ANALGESIC ACTIVITY (HOT-PLATE TEST)

Drug	"pA_2"	Time of maximum activity of drug (min)
M183	4·26	15
Methadone	4·20	15–30
Morphine	4·18	30–45

In an attempt to explain the failure of nalorphine to antagonize the action of pethidine on the hot-plate, the possible interference by an effect of the drug on body temperature was investigated. The relationship between skin temperature and

reaction time on the hot-plate is shown in Fig. 5, where it can be seen that a fall in temperature of 1° C may increase the reaction time by 2.7 sec. The relationship between the increase in reaction time above the control values before injection and the percentage analgesic response, obtained by the method described, is shown in

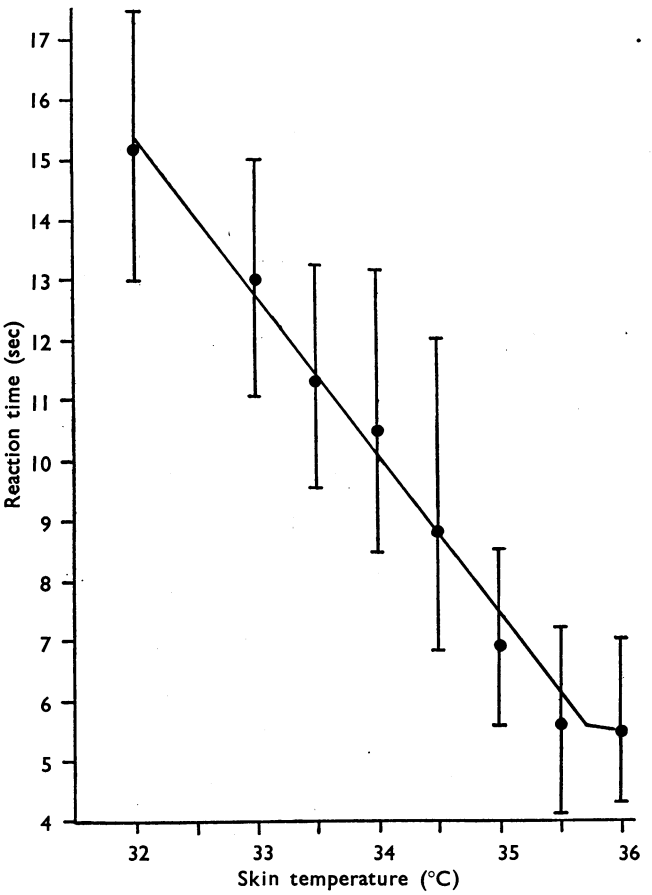

Fig. 5. Relationship between skin temperature and reaction time in mice. Abscissa: skin temperature (°C); ordinate: reaction-time (sec). Vertical lines indicate 95% confidence limits.

Fig. 6. Thus it was calculated that a fall in skin temperature of 1° C could increase the percentage analgesic response by about 11%. These findings provided a convenient quantitative basis from which to study the action of pethidine on skin temperature.

The effect of three drugs, pethidine, methadone and M183, on the skin temperatures of mice is shown in Table 5. At the doses of the drugs used for the measurement of analgesic activity, both pethidine and methadone lowered skin temperature. However, whereas the fall produced by methadone was antagonized by nalorphine, that given by pethidine was, if anything, increased.

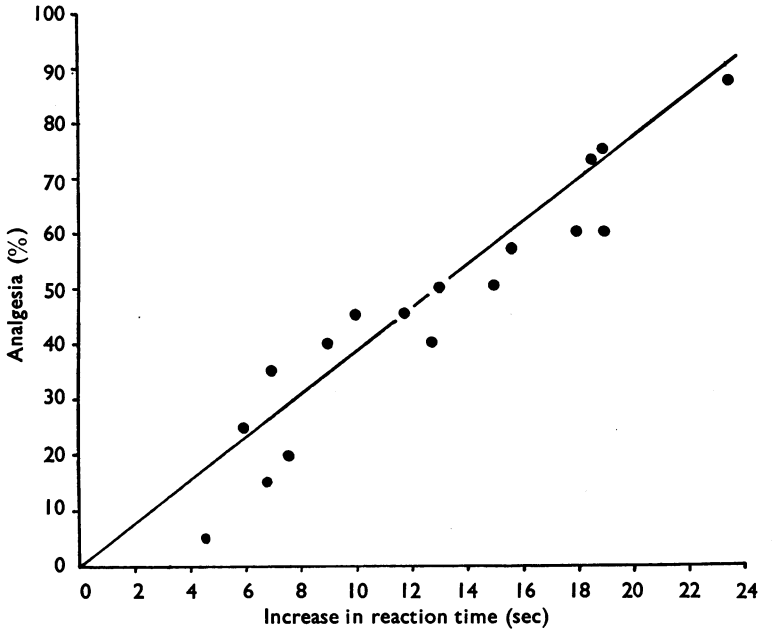

Fig. 6. Relationship between percentage response for analgesia and increase in reaction time above control value. Increase in reaction time of 1 sec is equivalent to 4% analgesia.

TABLE 5

EFFECT OF ANALGESIC DRUGS AND NALORPHINE ON SKIN TEMPERATURE IN MICE

* Denotes an increase in temperature. Doses of nalorphine (in parentheses) are in mg/100 g of body weight

Drug	Dose (mg)	Maximum fall in temperature (°C) after Drug alone	Nalorphine (0·05)	Nalorphine (0·1)	Nalorphine (0·2)
Pethidine	2	1·5	1·6	2·0	2·1
	3	1·5	1·8	1·6	2·5
	4	1·6	2·1	2·4	2·4
Methadone	0·5	2·2	0·5	0	—
	1·0	1·8	0·3	0·5*	0·5*
	2·0	0·6	0·0	0·1	—
M183	0·002	0·6	0·1*	0·0	—
	0·003	0·5*	0·8*	0·6	0·2*
	0·005	0·1	0·2	0·6	—

A correction was applied to the percentage responses for analgesia given by the doses of pethidine alone and together with nalorphine, based on the expected increase in the percentage response from a fall in temperature of 1° C, that had been calculated previously. The corrected dose-ratios are shown in Fig. 4.

In another series of experiments, nalorphine was injected 15 min before various doses of pethidine, and the percentage analgesic response determined. However, this did not significantly differ from the values obtained when pethidine and the antagonist were given simultaneously.

DISCUSSION

The results of the investigation of the action of nalorphine have shown that the same amount of antagonist was required to reduce the lenticular opacity effect of seven different analgesic drugs, the activities of which (ED50s) ranged from 2 μg to 5 mg. Since groups of animals were used in these experiments instead of the usual isolated organ preparations, the absolute concentration of nalorphine at the site of action was unknown. We therefore had to assume that it was proportional to the dose of antagonist injected, on a weight basis. Thus it was only possible to determine the equivalent of a pA_2 value, which was defined as "the negative log of the molar dose of nalorphine per 100 g of body weight, required to reduce the effect of a double dose of active drug to that of a single dose." In this way we were able to obtain "pA_2" values for each drug with nalorphine. This indicated that nalorphine antagonized the production of opacity by competing with the active drugs for essential receptor sites.

The "pA_2" values for the different analgesic drugs were almost identical, in spite of the fact that the times of peak activity of the drugs were not the same. These ranged from 30 to 75 min, so that, unless nalorphine was able to exert a constant effect throughout that time, it is likely that the absolute concentration of nalorphine varied. This might explain why the "pA_2" value for morphine was slightly lower than those for the other drugs, whose effects reached their peaks earlier. Thus it can reasonably be assumed that all the analgesic drugs that were used produce lenticular opacity by combining with similar receptors.

In this way it was also possible to demonstrate competitive antagonism between nalorphine and three drugs for their analgesic activity. Very similar "pA_2" values were obtained for morphine, methadone and M183, which closely followed those in the opacity test. However, we were unable to reduce quantitatively the analgesic activity of pethidine. This may have been due to our method of measuring "analgesic activity." In addition to the effect of these drugs in diminishing pain sensation with which one is primarily concerned, several other actions could complicate the final measurement of reaction time, on which the assessment of analgesia was based: for instance, a depression of the reaction time itself, as one would see with sedatives such as reserpine and chlorpromazine; an action on spinal reflexes, which morphine is known to depress (Herr, Nyiri & Venulet, 1952; Cook & Bonnycastle, 1953); and an action on body temperature. Unless each of these actions is antagonized to the same degree by nalorphine, one may fail to obtain a "pA_2" value.

Winter & Flataker (1953) have shown in the dog that, when the measurement of analgesia is based on the reaction to a heat stimulus, the increase in pain threshold after morphine may be largely accounted for by a lowering of skin temperature. Pethidine lowers rectal temperature in mice at the dose levels used in our experiments (Kopera & Armitage, 1954). We were able to show in the mouse that part of the "analgesic response" after pethidine was due to the fall in skin temperature. Furthermore, this action of pethidine was not prevented by the simultaneous administration of nalorphine. However, after a correction had been applied to the dose-ratios for pethidine, derived from the calculated contribution that could have been made

by the temperature factor, we were still unable to obtain a linear result. Thus, although the failure of nalorphine to antagonize the effect of pethidine on skin temperature may partially contribute to the measured analgesic activity when 0.1 to 0.2 mg/100 g of nalorphine was given, it cannot be the only explanation, even if allowance is made for the necessary assumptions made in the calculations of the correction factor. It would be of interest to see whether a similar result would still be obtained with pethidine if a different method of measuring analgesia, such as the tail-pressure method described by Bianchi & Franceschini (1954), were used.

Smith, Lehman & Gilfillan (1951) also reported a failure to antagonize completely the analgesic activity of pethidine with 1 mg/100 g of nalorphine in the rat, but they give no experimental details. On the other hand, Winter, Orahovats, Flataker, Lehman & Lehman (1954) were able to obtain complete antagonism in the rat with 0.1 mg/100 g, and, as in our experiments, nalorphine was injected immediately before the analgesic drug. The possibility was considered that the action of pethidine was more rapid than that of nalorphine, or that the analgesic was absorbed more rapidly than the antagonist. However, we were unable to obtain a greater antagonism of the analgesia by giving the nalorphine 15 min before pethidine.

In the absence of further evidence one must conclude that part of the effect of pethidine in increasing "pain threshold" as measured by the hot-plate method in mice is produced by a mechanism which differs from that of other analgesic drugs, and is insensitive to nalorphine.

The results obtained with several other morphine-like drugs are consistent with the hypothesis that nalorphine antagonizes both the analgesia and lenticular effect by competing with the active drugs for essential receptor sites.

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