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Morphine–Halothane Interaction in Rats

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The effects of morphine, halothane, and their various combinations on the purposeful movement (PM) response and the heart rate (HR) increase caused by noxious stimulation were studied in 250 rat experiments. Doses that block the PM and HR responses for the single agent and for combinations were determined with a probit procedure and compared with an isobolographic analysis. As was evidenced by the PM response, the combined anesthetic effect of morphine and halothane, with some deviations, may be defined as additive. It also was found that the combined administration of morphine and halothane results in an antagonism for suppression of the HR increase to noxious stimulation. Halothane antagonized morphine to a much greater extent than morphine to halothane. (Key words: Anesthetics, volatile: halothane. Analgesics: morphine. Interactions (drug). Potency, anesthetic: ED_{50}.)

IN THE LAST DECADE, narcotic analgesics have become extremely popular as anesthetic agents used alone and in combination with conventional general anesthetics. Investigations of narcotic–anesthetic combinations based on motor responses to noxious stimulation have shown that narcotics decrease the requirement for inhalational anesthetics. Saidman and Eger reported that morphine, given as premedication, decreased halothane MAC in surgical patients.[1] Hoffman and DiFazio showed that morphine, meperedine, and pentazocine produced a reduction of cyclopropane MAC in rats.[2] Murphy and Hug described the enflurane sparing effects of morphine, fentanyl, butorphanol, and nalbuphine in dogs.[3,4] The decrease in the requirement for an inhalational anesthetic with administration of a narcotic analgesic excludes the presence of absolute antagonism with regard to inhalational anesthetics but cannot differentiate between supraadditive, additive, or infraadditive types of interaction.

There is evidence that the sympathetic nervous system insufficiently is blocked with narcotic administration, and as a result, patients can experience hypertension and/or tachycardia during operations.[5,6] However, Roizen and associates[7] have reported that the combined administration of nitrous oxide (60 vol%) and morphine in a dose of 1.45 mg/kg could block an increase in arterial pressure in response to skin incision in five out of seven patients. Blockade of sympathetic responses to surgical stimulation is one of the goals of anesthesia; therefore, it is of importance to investigate effective ways to achieve this goal through the combined effect of various agents.

The purpose of this study was to define the type of interaction between morphine and halothane with regard to abolition of purposeful movement and heart rate responses to noxious stimulation. The interaction of morphine and halothane was analyzed with the isobolographic method.[8-10]

Methods

Two series of experiments on 250 male, Sprague–Dawley rats weighing 275–325 g were performed. In one series, morphine–halothane anesthetic interaction was investigated with the use of abolition of the purposeful movement (PM) response to noxious stimulation. In another series, we studied the morphine–halothane interaction for blockade of heart rate increase caused by noxious stimulation.

PM Response

Purposeful movement response was tested by the placement of a hemostat on the tail (pressure of 8 kg on the tail surface of 0.25 cm^2) for 60 s (stiffening, coughing, hyperventilating, or vocalizing were not considered).[11] The experiments were carried out in a clear chamber where oxygen or a halothane–oxygen mixture could be delivered (4 l/min). The rat's tail (for noxious stimulation) or hind leg (for morphine injection into the saphenous vein) could be extended from the chamber through a slot.

Halothane was vaporized in a Draeger vaporizer, and vapor concentration in the chamber was monitored continuously with a calibrated Beckman LB-2® infrared analyzer. Each rat was exposed to only one predetermined dose of halothane, morphine sulfate (Merck Co.), or a combination. In experiments with halothane administration, the animals were exposed to the agent for 30 min before the PM response testing. In experiments where morphine was the only agent used, the animals were kept in the chamber with oxygen for 15 min, then morphine was injected (intravenously over 10 s), and the PM response was tested after an additional 15 min. A time interval of 15 min was chosen after preliminary experiments in which peak action for morphine was determined by the increase in reaction time for the tail withdrawal reflex.[12] This time interval is in agreement with the published data of Dahlstrom and Paalzow.[13] In experiments where halothane and morphine were used in combination,

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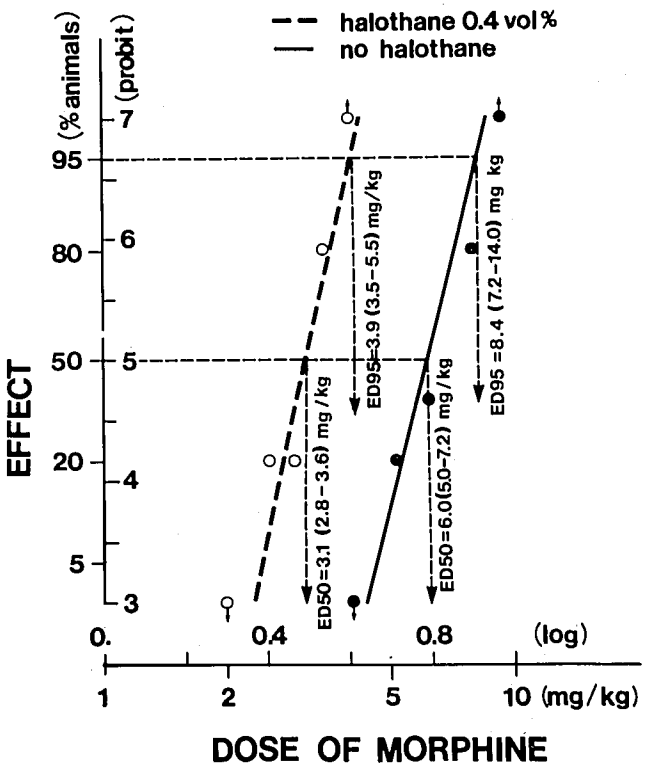

FIG. 1. Morphine dose–effect curves for purposeful movement caused by noxious stimulation. Along the vertical axis, the percentage of animals with lack of purposeful movement. Each circle represents the incidence of the response in a group of five animals at the indicated dosage. Closed circles = morphine alone (A series); Open circles = morphine administered in combination with halothane (B series). For calculation of dose–response curves, probit analysis was used; the indicated ED_{50} and ED_{95} values are based on this analysis.

the animals were exposed to the halothane–oxygen mixture for 15 min, then morphine was injected and an additional 15 min of continuing exposure to halothane was followed by the PM response test.

"Inspired" PM ED_{50} or PM ED_{95} values for halothane were determined as in our previous experiments.[14] Briefly, five groups of five rats constituted a halothane dose–effect curve that was calculated with the use of the probit method of statistical analysis.[15] The same approach was used to obtain morphine PM ED_{50} values (based on intravenous doses of the agent). In the single-agent series of experiments, the halothane dose range was from 1.0 vol% to 1.8 vol% and the morphine range from 4 mg/kg to 10 mg/kg. After determination of the PM ED_{50} value for morphine alone (A series), or halothane alone (E series), three series of experiments with combined morphine–halothane administration were performed. As with the single agent series of experiments, in each combined series of experiments, five groups of five animals were used to determine the quantal dose–effect curve for a drug combination. In one series of experiments (B series), the concentration of halothane was kept constant at 0.4 vol% (approximately ¼ of PM ED_{50}) in all five groups of the series. Only morphine was administered in different doses, equally spaced to give a range of doses that abolish movement response in none or all of the animals in a group (from 2 mg/kg to 4 mg/kg). In another series of experiments (D series), the dose of morphine was kept constant at 1.5 mg/kg (approximately ¼ of PM ED_{50}) in all five groups of the series, and halothane was administered in five different, equally spaced concentrations (from 1.1 vol% to 1.5 vol%). In the third series of experiments (C series), doses of both components of the combination were different in five groups. However, with the increased doses, the potency ratio between the components was kept constant at the level of 1:1. This means that for each fraction of PM ED_{50} of halothane, an equal fraction of PM ED_{50} of morphine was added. The halothane dose range was from 0.6 vol% to 1.5 vol% and the morphine dose range from 2.5 mg/kg to 6 mg/kg. PM ED_{50} values for the combined morphine–halothane series of experiments were calculated with the use of probit analysis, using the same approach as in the single agent series. An example of determination of ED values based on log-probit dose–effect curves is presented in figure 1 (A and B series). The isobolographic method was used as described elsewhere.[16] PM ED_{50} or PM ED_{95} values from all five series of experiments were plotted in the dose field, and isobols (line connecting equi-effective doses) were determined.

HR RESPONSE

Heart rate response was induced by the same noxious stimulation as for the purposeful movement response: placement of a hemostat on the tail for 60 s. The heart rate was obtained from an electrocardiogram. In addition to a Grass® 7P 44B cardiotachometer, heart rate also was counted by a special microcomputer-based cardiotachometer that counted the number of beats during a 15-s time interval with an output update every 5 s. Both the microcomputer-based cardiotachometer and the Grass cardiotachometer provided records of heart rate on a Grass® 7-D polygraph. Since the microcomputer-based cardiotachometer gave more precise measurements, we used the computer provided values for our calculations.

An increase in heart rate of 1% or less was determined as a positive effect (no response to the stimulation). With small doses of morphine or halothane, (or both) an increase in heart rate usually reached 10–12% from a baseline of 300–400 beats/min. Using this approach, we could obtain a quantal dose–effect curve of a graded type of reaction.[17] A heart rate increase of 1% or less was defined as a positive effect for two reasons. First, a change in the heart rate of less than 1% is difficult to differentiate from a normal beat to beat variation. Second, when making

the HR response quantal, we compared the precision of ED_{50} calculations for two levels of HR changes: 1 and 3% (see fig. 2). As a result, the probit calculations for the former end point were more precise (fiducial limits of 42–44 for a 1% HR increase *vs.* fiducial limits of 38–45 for a 3% HR increase, fig. 2).[18]

Each animal was exposed to a predetermined dose of halothane, morphine sulfate, or their combination. The total exposure time before testing the response to the noxious stimulation was 30 min. For the first 15 min, the animal was kept in a clear chamber where halothane could be delivered; then the hind leg of the rat was extended from the chamber and morphine in a predetermined dose (or saline) was injected into the saphenous vein, immediately followed by an intravenous injection of tubocurarine chloride (1 mg/kg). Volumes of the injected solutions were 0.5–1.0 ml for morphine (to keep the volume below 1.0 ml, the concentration of morphine was increased up to 100 mg/ml) and 0.25–0.35 ml for tubocurarine chloride. The duration of the injections was 10–15 s. After the injection of tubocurarine, an endotracheal tube was inserted with the use of a special laryngoscope,[19] and the animal was ventilated with a Harvard S680 Rodent® Respirator. The ventilation rate was maintained at 60/min with the tidal volume adjusted to maintain Pa_{CO_2} at 40 ± 5 mmHg (2.0–2.4 ml). In the experiments with halothane administration, its delivery was continued after intubation (through a bag and the respirator). The heart rate response was tested 15 min after injection of morphine and/or after 30 min of exposure to halothane.

HR ED_{50} values for halothane, morphine, and their combinations were determined as described above for the purposeful movement response. In two series of experiments, morphine (A series) and halothane (E series) were used alone and in three series of experiments (B, C, and D series) they were administered in combinations. All series consisted of five groups of five animals. The morphine dose range was from 3 mg/kg to 10 mg/kg (A series); the halothane dose range was from 1.8 vol% to 2.5 vol% (E series). In the B series of experiments, the concentration of halothane was kept constant at 0.5 vol% (approximately ¼ of the HR ED_{50}) in all five groups of the series. Only morphine was administered in different doses, equally spaced to give a range of doses that abolished the heart rate response in none or all of the animals in a group (dose range from 270 mg/kg to 330 mg/kg). In the D series of experiments, the dose of morphine was kept constant at 1.5 mg/kg (approximately ¼ of the HR ED_{50}) in all five groups of series, and halothane was administered in five different equally spaced concentrations (dose range from 1.5 vol% to 2.8 vol%). In the C series of experiments, doses of both components of the combination were different in the five groups. However, with an increase in the doses, the potency ratio between the components was kept constant at the level of 1:1. The halothane dose range in this series was from 1.5 vol% to 2.8 vol%, and the morphine dose range was from 4 mg/kg to 8 mg/kg. HR ED_{50} values for all five series of experiments were used for isobolographic analysis.

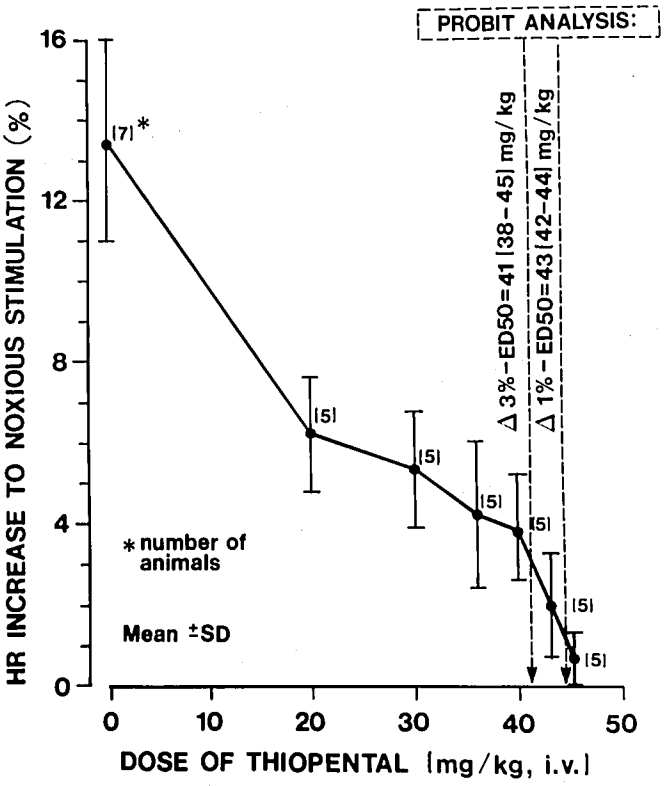

FIG. 2. Conversion of a graded heart rate response to a quantal response at two levels of heart rate change: 1 and 3%. Each point represents a separate group of five or seven rats. ED_{50} values were determined with the use of probit analysis at two levels of heart rate changes. Δ 3%—heart rate increase of 3% and less was defined as a positive effect; Δ 1%—heart rate increase of 1% and less was defined as a positive effect. The figure is based on the data obtained in rat experiments with thiopental.[18] See text for explanation.

The deviation of the isobol from the additive line was tested by determining *P* values for the distance of "combined" ED_{50} points from the additive line. All calculations were performed with the use of the probit procedure[15] on an IBM 370 computer.

Results

PM Response

The morphine–halothane ED_{50} isobol for the abolition of purposeful movement is presented in figure 3. The PM ED_{50} of morphine was 6.0 mg/kg (95% fiducial limits, 5.0–7.2); the PM ED_{50} of halothane was 1.36 vol% (95%

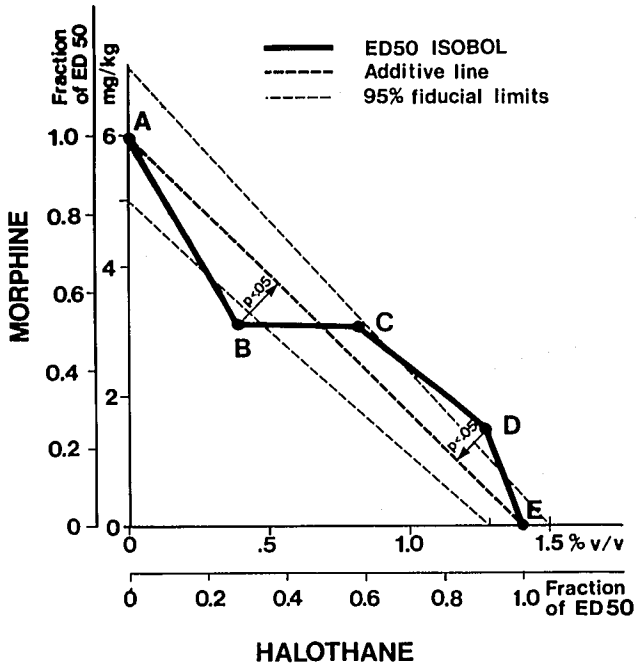

FIG. 3. ED_{50} isobologram for the interaction of morphine and halothane as characterized by abolition of purposeful movement caused by noxious stimulation. A and E—PM ED_{50} values for morphine and halothane alone (plotted on coordinates). B, C, and D—PM ED_{50} values for their combinations. The PM ED_{50} isobol has been generated by connecting adjacent PM ED_{50} points.

fiducial limits, 1.27–1.48). Each of these doses are shown on the respective single-drug dose coordinate of isobologram (points A and E). PM ED_{50} values for the three various combinations of morphine and halothane are within the dose field (points B, C, and D). The isobol interconnecting adjacent PM ED_{50} values has some deviation from the additive line joining single-drug PM ED_{50} doses. Point B deviates somewhat to the left of the additive line (supraadditive effect, $P < 0.05$); point D, on the contrary, deviates to the right (infraadditive, $P < 0.05$). To elucidate whether these deviations are more profound with the increase in the level of response to the agents, ED_{95} isobol also was determined (fig. 4). The ED_{95} isobol demonstrated principally the same type of changes, as did the ED_{50} isobol. Although point C on the ED_{95} isobol is rather remote from the additive line, the change was statistically insignificant (tendency for infraadditive effect). At point B, the ED_{95} isobol demonstrated a supraadditive interaction. The whole morphine dose–effect curves for B and A series of experiments is presented in figure 1. A comparison of the obtained PM ED_{50} doses for morphine–halothane combinations with the expected doses for an additive interaction is presented in table 1 in numeric form. The expected/observed ratios indicate only small deviations from the additive line.

HR Response

The morphine–halothane ED_{50} isobol for suppression of the heart rate increase is presented in figure 5. The HR ED_{50} value of morphine was 5.9 mg/kg (95% fiducial limits, 4.5–8.0); the HR ED_{50} value for halothane was 2.2 vol% (95% fiducial limits 2.0–2.4). Each of these doses are shown on the respective single-drug dose coordinate of the isobologram (points A and E). HR ED_{50} values for the three various combinations of morphine and halothane are within the dose field (points B, C, and D). The isobol interconnecting adjacent ED_{50} values significantly deviates to the top and right of the additive line joining single drug ED_{50} doses (infraadditive interaction). The most pronounced infraadditive interaction of morphine and halothane was present in series B of the experiments. Comparison of the A and B series gives the best illustration for the observed antagonism with high morphine–low halothane combination. Tables 2 and 3 present absolute data in the changes in heart rate in 25 experiments of each of these two series.

A comparison of the obtained HR ED_{50} doses for morphine–halothane combinations with the expected doses for additive interaction is presented in table 4 in numeric

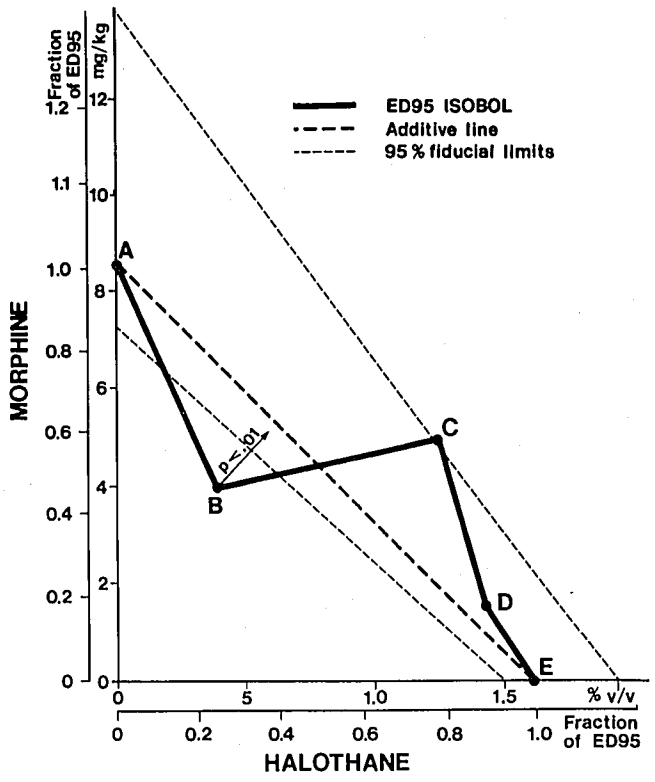

FIG. 4. ED_{95} isobologram for the interaction of morphine and halothane as characterized by abolition of purposeful movement caused by noxious stimulation. A and E—PM ED_{95} values for morphine and halothane alone. B, C, and D—PM ED_{95} values for their combination.

TABLE 1. Comparison of Equi-effective Doses of Morphine-Halothane Combinations at ED_{50} Level for Blockade of Purposeful Movement Caused by Noxious Stimulation

Series of Experiments	n	Equi-effective Dose (PM ED_{50}) of Morphine–Halothane Combinations					Expected Sum of Doses for Additive Interactions (Fractions)	Deviation from Additive Interaction (Expected/Observed Ratio)
		Morphine Component		Halothane Component		Sum of Fractions		
		Fraction of ED_{50}	Dose in mg/kg	Fraction of ED_{50}	Concentration in vol %			
A	25	1.00	6.0 (5.0–7.2)	0.00	0.0	1.0	—	—
B	25	0.52	3.1 (2.8–3.6)	0.28	0.4*	0.80	1.00	1.25 $P < 0.05$
C	25	0.55	3.3 (2.1–4.3)	0.57	0.8 (0.5–1.0)	1.12	1.00	0.89 NS
D	25	0.25	1.5*	0.93	1.3 (1.2–1.4)	1.18	1.00	0.85 $P < 0.05$
E	25	0.00	0.0	1.00	1.4 (1.3–1.5)	1.0	—	—

Fiducial limits are in parentheses.

* Dose (or concentration) was kept constant (see "Methods").

form. The table demonstrates that all tested combinations show a significant infraadditive effect for the abolition of the increase in heart rate in response to noxious stimulation. The expected/observed ratio that reflects deviation from an additive interaction reached its minimum, 0.02 ($P < 0.0001$), in the B series. With a decrease in the morphine component and an increase in the halothane component of the combination, the ratio decreased and was only 0.75 ($P < 0.01$) in the D series of experiments.

Discussion

The "inspired" PM ED_{50} value for halothane obtained in this study was 1.36 vol%, as compared with 1.1 vol% in our previous study.[14] The intensity of noxious stimulation in these two studies was different. In the previous experiments, the pressure on the tail was 1 kg on the surface of 0.25 cm^2, compared with 8 kg/0.25 cm^2 in this study. Thus, an 8-fold increase in the intensity of stimulation caused an approximately 20% increase of PM ED_{50} values for prevention of the purposeful movement response. This agrees well with the statement of Eger and co-authors that the intensity of stimulus beyond a certain strength has an insignificant effect on the MAC.[20]

It is known that rats are relatively resistant to the respiratory effect of morphine. In the experiments of Isom and associates,[21] morphine in doses of 10 and 20 mg/kg did not alter significantly the rats' (Sprague–Dawley) oxygen consumption; only doses of 40–160 mg/kg decreased the oxygen consumption up to 25% from the control level. In our pilot experiments (5, 10, 20, and 40 mg/kg of morphine were used), it was found that only morphine 40 mg/kg significantly increased Pa_{CO_2} (55–69 mmHg), which is in good agreement with the reported data. In the purposeful movement experiments, we used morphine only in a 3–10 mg/kg dose range; nevertheless, to counteract possible hypoxemia, we used oxygen.

Our PM ED_{50} value for morphine (6.0 mg/kg) is very close to those obtained with the Haffner method (tail-

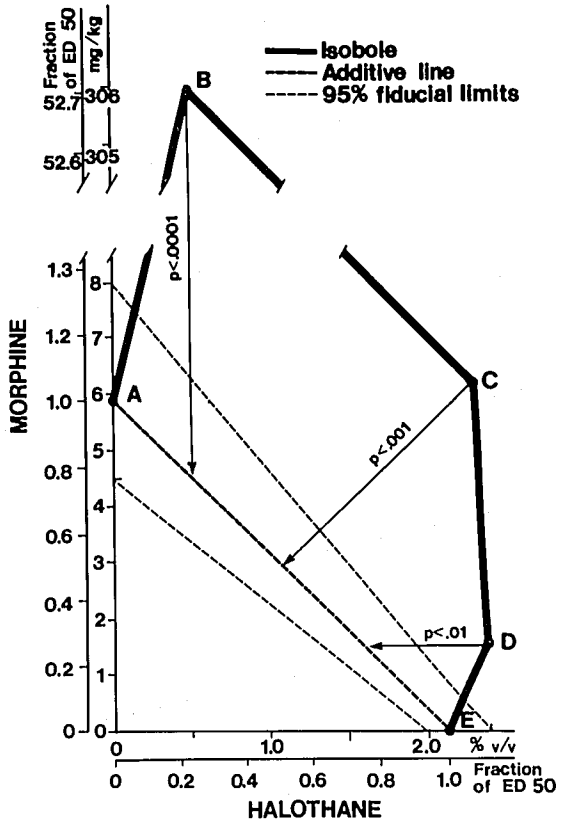

FIG. 5. ED_{50} isobologram for the interaction of morphine and halothane as characterized by abolition of the heart rate increase to noxious stimulation. A and E—HR ED_{50} values for morphine and halothane alone (plotted on coordinates); B, C, and D—HR ED_{50} values for combinations.

TABLE 2. Effect of Morphine on the Increase in Heart Rate Caused by Noxious Stimulation (Dose-Effect Data for A Series of Experiments)

Morphine Dose (mg/kg)	Animal Number	Baseline Heart Rate (beats/min)	Maximal HR Increase after Stimulation (beats/min)	Considered as Positive Effect
	1	265	25	No
	2	350	27	No
3	3	300	11	No
	4	280	15	No
	5	330	70	No
Positive/total ratio for the group—0/5				
	6	320	0	Yes
	7	290	27	No
4	8	310	12	No
	9	320	40	No
	10	390	9	No
Positive/total ratio for the group—1/5				
	11	235	1	Yes
	12	245	8	No
6	13	295	10	No
	14	295	12	No
	15	255	2	Yes
Positive/total ratio for the group—2/5				
	16	320	18	No
	17	275	3	Yes
8	18	300	0	Yes
	19	340	0	Yes
	20	325	0	Yes
Positive/total ratio for the group—4/5				
	21	340	0	Yes
	22	365	0	Yes
10	23	275	3	Yes
	24	275	0	Yes
	25	260	0	Yes
Positive/total ratio for the group—5/5				

Results of probit analysis for the series: Morphine HR ED_{50} = 5.9 (4.5–8.0)* mg/kg; HR ED_{95} = 11.3 (8.3–32.5) mg/kg.

* Fiducial limits.

clamping)—5.7 mg/kg[22]; 7.0 mg/kg[23]—or with the tail-flick test—6–8 mg/kg.[24] Close agreement between the above results suggests that the purposeful movement response used in our study correctly reflected the morphine analgesic potency. The above data also may be regarded as additional evidence that it is possible to block movement response to a strong, painful stimulation with the use of morphine alone, without the addition of an inhalational anesthetic.

Isobolographic analysis showed that the combination of morphine with halothane gives relatively small deviations from additive interaction for the abolition of movement response to noxious stimulation. Deviation from simple addition was directed to opposite sides at the upper and lower parts of the isobologram: with the high morphine–low halothane combination, we observed some supraadditive effect (synergism), and with a high halothane–low morphine combination, a small infraadditive effect (antagonism). Since it has been shown by Eger[11] that halothane MAC decreases when Pa_{CO_2} exceeds 90 mmHg, we speculated that the slight supraadditive effect obtained in our experiments at point B (see fig. 3) might be due to a CO_2 increase due to respiratory depression caused by a high morphine–low halothane combination. To check this assumption, we measured Pa_{CO_2} in rats (with a preimplanted fluid-filled catheter in the carotid artery) after exposure to a combination of halothane (0.4 vol% in oxygen) and morphine (3 mg/kg). Pa_{CO_2} obtained in these experiments (56 ± 4 mmHg, n = 6) was not high enough to explain a supraadditive effect.

Saidman and Eger have shown that morphine (8–15 mg, sc) used as a premedication in surgical patients decreased halothane MAC by 9%.[1] It also has been reported that morphine caused a very significant reduction in the

TABLE 3. Combined Effect of Morphine and Halothane on the Increase in Heart Rate Caused by Noxious Stimulation (Dose–Effect Data for B Series of Experiment)

Doses	Animal Number	Baseline Heart Rate (beats/min)	Maximal HR Increase after Stimulaiton (beats/min)	Considered as Positive Effect
Morphine	1	400	18	No
270 mg/kg	2	400	8	No
Halothane	3	370	10	No
0.5 vol%	4	370	6	No
	5	410	16	No
Positive/total ratio for the group—0/5				
Morphine	6	380	9	No
300 mg/kg	7	380	11	No
Halothane	8	405	12	No
0.5 vol%	9	365	0	Yes
	10	430	12	No
Positive/total ratio for the group—1/5				
Morphine	11	390	10	No
310 mg/kg	12	360	38	No
Halothane	13	380	4	Yes
0.5 vol%	14	420	4	Yes
	15	390	8	No
Positive/total ratio for the group—2/5				
Morphine	16	390	3	Yes
320 mg/kg	17	350	32	No
Halothane	18	390	0	Yes
0.5 vol%	19	380	0	Yes
	20	410	2	Yes
Positive/total ratio for the group—4/5				
Morphine	21	330	0	Yes
330 mg/kg	22	355	4	Yes
Halothane	23	375	4	Yes
0.5 vol%	24	390	0	Yes
	25	375	0	Yes
Positive/total ratio for the group—5/5				

Results of probit analysis for the series: Morphine HR ED_{50} = 306 (297–316)* mg/kg; HR ED_{95} = 318 (311–405) mg/kg.

* Fiducial limits.

TABLE 4. The Comparison of Equi-effective Doses of Morphine–Halothane Combinations at ED_{50} Level for Blockade of the Heart Rate Increase Caused by Noxious Stimulation

Series of Experiments	n	Equi-effective Doses (HR ED_{50}) of Morphine–Halothane Combinations					Expected Sum of Doses For Additive Interaction (Fractions)	Deviation from Additive Interaction (Expected/Observed Ratio)
		Morphine Component		Halothane Component				
		Fraction of ED_{50}	Dose in mg/kg	Fraction of ED_{50}	Concentration in vol%	Sum of Fractions		
A	25	1.00	5.9 (4.5–8.0)	0.00	0.0	1.00	—	—
B	25	51.91	306.0 (297–316)	0.23	0.5*	52.14	1	0.02 $P < 0.0001$
C	25	1.05	6.2 (5.2–7.4)	1.04	2.3 (2.0–2.7)	2.09	1	0.48 $P < 0.001$
D	25	0.25	1.5*	1.09	2.4 (2.1–2.7)	1.34	1	0.75 $P < 0.01$
E	25	0.00	0.0	1.00	2.2 (2.0–2.4)	1.00	—	—

Fiducial limits in parentheses.

* Dose (or concentration) was kept constant (see "Methods").

cycloproprane requirements in dogs[25,26] and rats.[2] Interaction between morphine and nitrous oxide in rats resulted in an increase in the number of anesthetized animals.[27] Calderone found no significant change in blood concentration of diethyl ether necessary for surgical anesthesia in dogs premedicated with morphine (2–5 mg/kg, sc).[28] Murphy and Hug have reported that morphine produced a reduction in enflurane requirements in dogs.[4] However, when they used high morphine–low enflurane combinations, even 27 mg/kg morphine could not block the movement response to noxious stimulation without the addition of 0.69 vol% of enflurane (end-tidal concentration). It is very difficult to compare our results with those of Murphy and Hug. They are different in at least three aspects: species (dogs *vs.* rats); agents (enflurane *vs.* halothane); and methods (reduction in anesthetic requirements *vs.* isobolographic analysis). The latter is the most important, since only the isobolographic method requires measurement of the effect of both components of the combination given separately. Murphy and Hug did not investigate the effect of morphine given alone, and we could not find in the literature appropriate information obtained in dog experiments. If morphine ED_{50} for purposeful movement in dogs is close to 5 mg/kg, the results by Murphy and Hug indicate an antagonism between morphine and enflurane at some dose ratios. However, if the morphine ED_{50} value is in the region of 50 mg/kg, their data indicates a supraadditive interaction.

In our experiments, the interaction between morphine and halothane with regard to movement response was mostly additive, and this does not contradict the results of the studies that demonstrated a decrease in anesthetic requirements with the use of morphine. When the effect of morphine administered alone is not measured, a decrease in anesthetic requirements effectively may exclude only the presence of absolute antagonism (to an anesthetic). Relative antagonism (the effect of the anesthetic–narcotic combination is less than the arithmetic sum of the effects of the components given alone, however, more than the effect of one of the components) cannot be ruled out. The additive and supraadditive effects also cannot be differentiated.

Our morphine ED_{50} value (5.9 mg/kg) for abolition of the increase in heart rate was not different from the morphine ED_{50} value for abolition of the purposeful movement response (6.0 mg/kg). At the same time, the halothane ED_{50} value (2.2 vol%) for abolition of the increase in heart rate was 57% higher than the ED_{50} for abolition of the purposeful movement response (1.4 vol%). It is possible to suggest that such a difference between morphine and halothane is due to the fact that morphine, in contrast to halothane, selectively affects afferent CNS systems and, therefore, inhibits common, initial parts of pathways for somatic and sympathetic responses. As a result, morphine inhibits both responses at the same doses.

The unexpected result of this study was profound antagonism between morphine and halothane for suppression of the heart rate increase to noxious stimulation. This antagonism was not uniform: halothane antagonized morphine to a much greater extent than morphine to halothane. The expected/observed ratio of HR ED_{50} values that reflects deviation from additive interaction reached 0.02 with low halothane–high morphine combination and only 0.75 with low morphine–high halothane combination. In fact, the low morphine–high halothane interaction did not deviate very significantly from relative antagonism (a type of infraadditive interaction when the halothane requirement is not increased by morphine). At

the same time, halothane used in a low concentration (0.5 vol%) increased morphine requirements to block the rise in heart rate 52 times. While considering profound weakening of the effect of morphine by halothane, an analogous phenomenon related to the dramatic change in the strength of morphine action should be mentioned. It has been shown in mice that after transection of the spinal cord, the noxious stimulus continues to cause the tail-flick reflex; however, doses of morphine required to block this reflex was 120 mg/kg as compared with 6–8 mg/kg without cord transection.[29] A decrease in the effect of morphine in animals whose spinal cords have been transected has been reported by a number of investigators. Irwin and associates found this phenomenon in rats with the use of the "tail flick" method.[30] Takagi and co-authors demonstrated in spinal rabbits that doses of morphine should be increased to inhibit evoked responses in the lamina V dorsal horn neurons as compared with the intact animals.[31] Hanaoka *et al.* confirmed these results in cats with the use of a similar method.[32] The above analogy may suggest that halothane in some way removes a modulating effect that controls HR response to painful stimulation.

Do the above results of morphine–halothane antagonism with regard to the HR response contradict our knowledge on the combined effect of morphine and halothane on hemodynamic responses to painful stimulation in patients undergoing surgery? In clinical practice, the usual combination is that of low morphine–high halothane. As we can see from the segment of the isobologram between points D and E (fig. 5), there is no statistical significance in the difference between the HR ED_{50} doses of halothane given alone as compared with those combined with small doses of morphine. These data do not contradict clinical experience on the effect of halothane in combination with small doses of morphine. The most profound morphine–halothane antagonism found in our experiments was with high morphine–low halothane combination. Frequent hypertension and tachycardia in anesthesia based on high doses of morphine are well known and regarded not as pharmacologic responses to morphine but "responses to noxious stimulation that are not suppressed by morphine."[6] Although rat experimental data and human clinical experience are rather difficult to correlate, it is also difficult to exclude the possibility that antagonism between morphine and one of the agents with general anesthetic properties given before or during morphine anesthesia in surgical patients may be responsible for an incomplete suppression of heart rate or blood pressure responses to noxious stimulation.

It is interesting to compare the morphine–halothane interaction for the heart rate increase with their interaction for the purposeful movement response. With regard to the heart rate increase, we have found a profound infraadditive interaction. At the same time, when the purposeful movement end point was used, infraadditive interaction was small and observed only with high halothane–low morphine combination. The movement response to a noxious stimulation is a commonly accepted index of anesthesia, and it shows that the combined anesthetic effect of morphine and halothane, with some slight deviations, may be defined as additive. Thus, the morphine–halothane interaction with regard to the heart rate end-point was very different from that for the purposeful movement end-point. It is possible to regard this difference from the two following positions. One viewpoint may be based on the suggestion that anesthesia has different components.[33] The blockade of purposeful movement (somatic response) and blockade of heart rate increase (sympathetic response) may be viewed as different components of anesthesia, which respond differently to morphine–halothane combinations. According to another viewpoint, blockade of the movement response reflects the anesthetic process and abolition of the heart rate response does not. Therefore, the interaction of morphine and halothane with regard to a nonanesthetic process (suppression of the heart rate response) may be quite different from that for an anesthetic process.

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References

1. Saidman LJ, Eger EI, II: Effect of nitrous oxide and of narcotic premedication on the alveolar concentration of halothane required for anesthesia. ANESTHESIOLOGY 25:302–306, 1964
2. Hoffman JC, DiFazio CA: The anesthesia-sparing effect of pentozocine, meperidine, and morphine. Arch Int Pharmacodyn 186:261–268, 1970
3. Murphy MR, Hug CC: The anesthetic potency of fentanyl in terms of its reduction of enflurane MAC. ANESTHESIOLOGY 52:485–488, 1982
4. Murphy MR, Hug CC: The enflurane sparing effect of morphine, butorphanol, and nalbuphine. ANESTHESIOLOGY 57:489–492, 1982
5. Lowenstein E: Morphine "anesthesia"—A perspective. ANESTHESIOLOGY 35:563–565, 1971
6. Hug CC: Pharmacology—anesthetic drugs, Cardiac Anesthesia. Edited by Kaplan JA, New York, Grune and Stratton, 1979, pp 19–24
7. Roizen MF, Horrigan RW, Frazer BM: Anesthetic doses blocking adrenergic (stress) and cardiovascular responses to incision—MAC BAR. ANESTHESIOLOGY 54:390–398, 1981
8. Loewe S, Muischnek H: Ueber Konbinationswirjungen. I. Mitteilung: Hilfsmittel der Fragestellung. Naunym Schmiedebergs Arch Pharmacol 114:313–326, 1926
9. Loewe S, Aldous RA, Fox SR, Johnson DG, Perkins W: Isobols of dose–effect relations in the combination of trimethadione and pentylenetetrazole. J Pharmacol Exp Ther 113:475–480, 1955
10. Smith NT: Use of isobolograms in anesthesia. Anesth Analg 45:467–473, 1966

11. Eger EI II: Anesthetic uptake and action. Baltimore, Williams and Wilkins, 1974, p 2
12. Janssen PAJ, Neimegeers CJE, Dony JGH: The inhibitory effect of fentanyl and other morphine-like analgesics on the warm water induced tail withdrawal reflex in rats. Arzneimittelforsch 13:502, 1963
13. Dahlstrom BE, Paalzow L: Pharmacokinetics of morphine in relation to analgesia: effects of routes of administration, Factors Affecting the Action of Narcotics. Edited by Manara AL, Samanin R. New York, Raven Press, 1978, pp 233–241
14. Kissin I, Morgan PL, Smith LR: Comparison of isoflurane and halothane safety margins in rats. ANESTHESIOLOGY 58:556–561, 1983
15. Finney DJ: Probit analysis. London, Cambridge University Press, 1952
16. Kissin I, McGee T: Hypnotic effect of thiopental-lidocaine combination in the rat. ANESTHESIOLOGY 57:311–313, 1982
17. Goldstein A, Aronow L, Kalman SM: Principles of Drug Action: The Basis of Pharmacology. New York, John Wiley and Sons, 1974, p 188
18. Kissin I, McGee T, Smith LR: The indices of potency for intravenous anesthetics. Can Anaesth Soc J 28:585–589, 1981
19. Morgan PL: A modified laryngoscope blade for rat intubation. ANESTHESIOLOGY 57:431, 1982
20. Eger EI, II, Saidman LJ, Brandstater B: Minimum alveolar anesthetic concentration: a standard of anesthesia potency. ANESTHESIOLOGY 26:756–763, 1965
21. Isom GE, Nelson RB, Edlin AI: A comparison of the lethal and respiratory effects of morphine in Long–Evance and Sprague–Dawley rats. Arch Int Pharmacodyn 182:130–138, 1969
22. Bianchi C, Franceschini J: Experimental observations on Haffner's method for testing analgesic drugs. Br J Pharmacol 9:280–284, 1959
23. Kissel JW, Albert JR, Boxill GC; The pharmacology of prodilidine hydrochloride, a new analgetic agent. J Pharmacol Exp Ther 134:332–340, 1961
24. Dewey WL, Harris LS, Howes JF, Nuite JA: The effect of various neurochemical modulators on the activity of morphine and the narcotic antagonists in the tail-flick and phenylquinone test. J Pharamacol Exp Ther 175:435–442, 1970
25. Seevers BH, Meek WJ, Rovenstine EA: A study of cyclopropane anesthesia with special reference to gas concentrations, respiratory and electrocardiographic changes. J Pharmacol Exp Ther 51:1–17, 1934
26. Robbins BH, Baxter JH, Fitzhugh OG: Studies of cyclopropane. V. The effect of morphine, barbital and anytal upon the concentration of cyclopropane in the blood required for anesthesia and respiratory arrest. J Pharmacol Exp Ther 65:136–142, 1939
27. Barlow OW, Stormont MF: The premedication values of morphine, codeine, papaverine, narcotine and pantopon in relation to nitrous oxide anesthesia. J Pharmacol Exp Ther 46:141–156, 1932
28. Calderone FA: Studies on ether dosage after pre-anesthetic medication with narcotics (barbiturates, magnesium sulphate and morphine). J Pharmacol Exp Ther 55:24–38, 1935
29. Dewey WL, Snyder JW, Harris LS, Howes JF: The effect of narcotics and narcotic antagonists on the tail-flick response in spinal mice. J Pharm Pharmacol 21:548–550, 1969
30. Irwin S, Houde RW, Bennett DR, Hendershot LC, Seevers MH: The effects of morphine, methadone and meperidine on some reflex responses of spinal animals to nociceptive stimulation. J Pharmacol Exp Ther 101:132–143, 1951
31. Takagi H, Satoh M, Doi T, Kawasaki K, Akaike A: Indirect and direct depressive effects of morphine on activation of lamina V cell of the spinal dorsal horn induced by intra-arterial injection of bradykinin. Arch Int Pharmacodyn 221:96–104, 1976
32. Hanaoka K, Ohtani M, Toyooka M, Dohi S, Ghazisadi K, Taub A, Kitahata LM: The relative contribution of direct and supraspinal descending effects upon spinal mechanisms of morphine and analgesia. J Pharmacol Exp Ther 207:476–484, 1978
33. Woodbridge PD: Changing concepts concerning depth of anesthesia. ANESTHESIOLOGY 18:536, 1959