Respiratory Depression Associated with Relief of Pain by Narcotics

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Respiratory depression associated with relief of pain by meperidine was measured in 37 patients after upper abdominal or thoracic surgical operations. Pain relief was associated with a 10 per cent decrease in minute volume, an increase of 2.0 mm. Hg in P_{aCO_2} during breathing of air and a 3.4 mm. Hg displacement of the CO_2 response curve to the right (respiratory depression). In three of eight patients a placebo produced moderate to complete pain relief without depression of respiration. These data suggest that meperidine depresses the respiration of postoperative patients at least as much as respiration of healthy subjects, and that pain does not antagonize the respiratory depressant activity of meperidine.

ALL POTENT ANALGESICS produce significant respiratory depression when given to healthy subjects without pain. Despite this, obvious respiratory depression following therapeutic doses of analgesics given to postoperative patients is rare. Eckenhoff and Oech [1] suggested that under some circumstances pain may antagonize the respiratory depression produced by narcotics and that data which quantify respiratory depression relate only to the circumstances under which they were obtained. On the other hand, clinical opinion suggests that relief of pain may actually improve respiration following upper abdominal and thoracic surgical operations.[2] In fact, some investigators have used the increase in vital capacity as an index of analgesic potency.[3, 4] The relationship of narcotic-induced respiratory depression in healthy subjects to respiratory depression by narcotics in patients with postoperative pain has never been defined. This investigation was undertaken, therefore, to examine this relationship.

Methods

Patients were studied following major thoracic or upper abdominal surgery. The initial group of 23 patients was studied between 90 minutes and six hours after operation. A second group of 14 patients was studied on the first postoperative day in order to enlist their cooperation in obtaining carbon dioxide response curves. Halothane was the primary anesthetic agent in all patients, and all were given 50–75 mg. meperidine (Demerol) or 8–10 mg. morphine 60 to 90 minutes before operation. Duration of anesthesia was less than three hours in all patients.

DAY OF OPERATION

The characteristics of the patients are presented in table 1. In all patients a radial artery was cannulated during operation and the cannula remained in place after operation. When patients were sufficiently awake, their subjective pain was graded by an observer (medical student) as none, slight, moderate, or severe, according to his evaluation of the patients' statements. If pain was moderate or severe, an arterial blood sample was drawn. Meperidine was then slowly administered intravenously in 10- or 15-mg. increments with 15 minutes between doses until significant alleviation of pain occurred (pain was none or slight or "most" of the pain was gone). A second arterial blood sample was drawn 5–11 minutes after the last injection of meperidine. All but five patients were breathing oxygen by mask both times blood samples were drawn. Blood pressure and heart rate were recorded before and after meperidine.

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TABLE 1. Characteristics of Patients Studied on the Day of Operation

	Age	Sex	Operation	Inspired Gas	Hours after Operation	I.V. Meperidine (mg.)
Abdominal						
	43	M	Bilateral aortofemoral graft	Air	1.2	30
	61	M	Bilateral aortofemoral graft	O_2	1.5	30
	68	M	Bilateral aortoiliac graft	O_2	2.0	30
	50	M	Bilateral aortofemoral graft	O_2	1.5	30
	62	M	Resection abdominal aneurysm	O_2	3.5	15
	61	M	Bilateral aortoiliac graft	O_2	2.0	30
	35	M	Bilateral aortoiliac graft	Air	3.7	15
	58	M	Bilateral aortoiliac graft	O_2	1.5	30
	69	M	Resection abdominal aneurysm	Air	3.3	15
	64	M	Resection abdominal aneurysm	O_2	5.3	30
	71	M	Bilateral aortoiliac graft	O_2	2.5	30
	65	M	Resection abdominal aneurysm	O_2	2.2	30
Thoracic						
	60	F	Mitral commissurotomy	O_2	4.2	30
	18	M	Division patent ductus	O_2	2.0	30
	28	M	Aortic valve replacement	O_2	5.3	30
	23	F	Closure of VSD	Air	3.5	30
	28	M	Closure of ASD	Air	4.3	15
	40	M	Mitral valve replacement	O_2	6.2	30
	53	M	Aortic valve replacement	O_2	3.8	15
	25	F	Pericardiectomy	O_2	2.0	30
	63	F	Insertion of pacemaker	O_2	1.8	30
	65	M	Mitral valve replacement	O_2	4.0	30
	66	M	Resection ascending aortic aneurysm	O_2	3.8	30

First Postoperative Day

The characteristics of the patients are presented in table 2. When patients were believed to have moderate pain, they were requested to breathe through a rubber mouthpiece to which a Wright ventilation meter was attached by an anesthesia breathing tube yoke or Y-adapter. This system for obtaining car-

TABLE 2. Characteristics of Patients Studied on First Postoperative Day*

	Age	Sex	Operation	Hours after Operation	Relief after Placebo	I.V. Meperidine (mg.)
Abdominal						
	50	M	Repair hiatus hernia	23	—	40
	58	M	Bilateral aortofemoral graft	24	—	40
	51	M	Bilateral aortoiliac graft	23	None	40
	68	M	Repair hiatus hernia	26	Complete	Not given
	51	M	Renal artery bypass graft	25	None	30
	51	M	Repair hiatus hernia	21	Moderate	30
	59	M	Bilateral aortoiliac graft	25	Moderate	20
Thoracic						
	55	M	Aortic valve replacement	27	—	20
	50	F	Closure of VSD	22	—	30
	31	M	Aortic valve replacement	25	—	30
	37	F	Mitral commissurotomy	24	—	40
	22	M	Resection coarctation	17	None	40
	38	F	Closure of ASD	23	None	30
	19	M	Closure of VSD	26	Slight	20

* All patients breathed air with and without a rebreathing tube.

TABLE 3. Minute Volume of Ventilation ($\dot{V}_E$) and Respiratory Rate (f) in 14 Postoperative Patients Studied on the First Postoperative Day before and after Intravenous Meperidine

	No. of Patients	Before Meperidine		After Meperidine	
		f	$\dot{V}_E$	f	$\dot{V}_E$
Abdominal operations	7	17.3 ± 1.87	10.3 ± 1.29	17.7 ± 1.39	9.2 ± 0.82
Thoracic* operations	7	28.7 ± 2.32	12.8 ± 1.19	25.9 ± 2.55	11.7 ± 1.31
Total	14	23.0 ± 1.44	11.6 ± 0.84	21.8 ± 1.40	10.5 ± 0.75†

* Only six patients received meperidine.
† Significant drug effect at $P < 0.05$.

bon dioxide response curves by use of a face mask has been described by Edelist and Zauder.[5] The third limb of the yoke was used as an oxygen inflow port. The dead-space of this system was 90 ml. A nose clip was applied and oxygen flowed into the yoke at 500 ml./min. After 2–3 minutes of breathing to permit patients to accommodate to this system, minute volume of respiration ($\dot{V}_E$) and respiratory rate (f) were measured for one minute; an arterial blood sample was drawn during the last 20 seconds. Immediately, a rebreathing tube (44 inches long, 450-ml. volume) was added to the ventilation meter to induce hypercarbia. After 2–4 minutes of rebreathing, which varied according to the patient's tolerance to respiratory stimulation, $\dot{V}_E$ and f were again measured for one minute and arterial blood was drawn. Meperidine was then administered to six patients as described above, and the procedure was repeated 15 minutes after the last injection of meperidine. A placebo was given to eight patients and the measurements were repeated in five of them. Meperidine was then given to seven of the eight patients and the measurements were repeated. Drugs were not administered in a blind fashion. Arterial samples were collected

TABLE 4. Arterial Blood Gases in Postoperative Patients before and after Intravenous Meperidine with Relief of Pain

		No. of Patients	Before Meperidine		After Meperidine	
			P_{ACO_2} mm. Hg	P_{AO_2} mm. Hg	P_{ACO_2} mm. Hg	P_{AO_2} mm. Hg
Day of Operation	Abdominal* operations	12	39.4 ± 1.51	121 ± 15.3	41.0 ± 1.77	117 ± 14.3
	Thoracic†	11	39.8 ± 1.40	136 ± 15.4	42.3 ± 1.22§	163 ± 25.2
First Postoperative Day	Abdominal operations	7	40.1 ± 1.48	73.4 ± 2.23	41.7 ± 1.60	75.4 ± 2.93
	Thoracic‡ operations	7	37.4 ± 2.40	81.3 ± 7.34	39.6 ± 2.27§	83.9 ± 7.96
	Total	37	39.3 ± 0.80	109.0 ± 6.67	41.3 ± 0.82¶	116.6 ± 8.67

* Includes three patients who breathed room air.
† Includes two patients who breathed room air.
‡ Only six patients received meperidine.
§ Significant drug effect at $P < 0.05$.
¶ Significant drug effect at $P < 0.01$.

TABLE 5. Slope of Carbon Dioxide Response Curve before and after Placebo and Meperidine

(l./min./mm. Hg Pa_{CO_2})

	Placebo			Meperidine		
	No. of Patients	Before	After	No. of Patients	Before	After
Abdominal operations	3	4.22	2.37	6	2.76 ± 0.40	2.27 ± 0.62
Thoracic operations	2	1.69	1.38	7	2.56 ± 0.99	1.95 ± 0.99
All patients	5	2.96 ± 0.80	1.88 ± 0.43*	13	2.66 ± 0.54	2.11 ± 0.58

* Significant drug effect at $P < 0.05$.

anaerobically in heparinized syringes and analyzed immediately. Carbon dioxide tension (Pa_{CO_2}) was determined at 38° C. using a modified Severinghaus electrode, and oxygen tension (Pa_{O_2}) was measured with a modified Clark electrode.

Data were plotted as a stimulus response (Pa_{CO_2}–V_E) curve for each patient. The equation for the pre-drug curve was calculated and the slope was applied to the post-drug curve to measure displacement of parallel curves in terms of mm. Hg Pa_{CO_2}.[6] When a placebo was given before meperidine and the response curve determined, displacement by meperidine from the placebo curve was determined. The slopes of all post-drug curves were also calculated and compared. The *t* test for paired replicates or for comparison of group means was used for statistical evaluations, and results were expressed as mean ± standard error of the mean.

Results

Only blood gases were measured in patients studied on the day of operation. Blood gases, f and V_E with and without rebreathing were measured in patients studied on the first postoperative day. No significant differences in control values for Pa_{CO_2} were found among patients studied on the different days or among patients having abdominal in contrast to thoracic operations. Except for a significantly higher respiratory rate in patients studied on the first postoperative day after thoracic operations ($P < 0.01$), no significant differences in any measure which could be compared were found between patients having abdominal and those having thoracic operations. Since the responses to placebo and meperidine were not different when compared for site of operation or day of study, the data were pooled for presentation. In the tables, however, they are presented by subgroups.

RESPIRATION DURING MODERATE PAIN

Before treatment, 33 patients complained of moderate pain, one of severe pain, and three of slight pain which became severe with motion. All patients complained of increased pain on moving or deep breathing. Despite this degree of pain, hypoventilation was not prominent. Both V_E and f (table 3) were greater than accepted normal values or predicted values for age and surface area.[7] Mean Pa_{CO_2} values suggested hypocarbia rather than hypercarbia (table 4). Eight patients had Pa_{CO_2} values less than 35 mm. Hg, and only five had values exceeding 45 mm. Hg. The highest value observed was 47.5 mm. Hg. The slope of the CO_2 response curve in patients studied on the first postoperative day was 2.66 l/min./mm. Hg (table 5), and was somewhat greater than values usually observed in healthy subjects.[6] The significance of this observation is doubtful, however, in view of the difficult circumstances under which these curves were obtained, in contrast to similar curves for healthy subjects. Perhaps any difference could be accounted for in part by higher deadspace ventilation secondary to more rapid respiration in the patient group.

The Pa_{O_2} data (table 4) could not be pooled, since most patients studied on the day of operation were breathing oxygen by mask and

the patients studied on the first postoperative day had the added deadspace of the respiratory apparatus. Even with added deadspace and the small amount of supplemental oxygen, only four of 14 patients had Pa_{O_2} values less than 70 mm. Hg, and Pa_{O_2} values in the five patients breathing room air on the day of operation were 61, 72, 72, 82, and 86 mm. Hg. The lowest Pa_{O_2}, 54 mm. Hg, occurred in a patient whose Pa_{CO_2} was 29.3 mm. Hg on the day after a thoracic operation.

Effect of Meperidine

Meperidine produced significant decreases in minute volume (table 3) and significant increases in Pa_{CO_2} (table 4), but no significant change in respiratory rate. The increase in Pa_{CO_2} was not associated with a decrease in Pa_{O_2}. In fact, the only change in Pa_{O_2} of any magnitude was the insignificant increase of 27 mm. Hg in the thoracic group on the day of operation. The mean displacement of the CO_2 response curve by meperidine (table 6) was 3.3 mm. Hg in 13 subjects ($P < 0.01$), and although the mean slope also decreased (table 5) this change was not sufficiently large or consistent for significance. The mean values for all 13 patients in whom the CO_2 response curve was determined before and after meperidine are presented in figure 1.

Relief of pain by meperidine was not associated with hypotension, tachycardia, or bradycardia in any patient. Neither systolic nor diastolic nor mean blood pressure changed significantly after meperidine. An insignificant increase in heart rate of 5.3 beats/min. followed administration of meperidine. This has been observed by others.[8]

Response to Placebo

Three of eight patients (37 per cent) reported moderate to complete postoperative relief of pain following administration of a placebo. This incidence is in accord with many previous observations. In two patients, it was not possible to obtain a response curve after placebo because of the severity of pain. One patient who reported moderate relief of pain could not tolerate the increased pain of respiratory stimulation from rebreathing. Response curves were therefore obtained for only five patients after administration of a placebo. Except for a decrease in slope (table 5) no significant change occurred in any measure of respiration after the placebo. A comparison of the data of the two patients with relief of pain with those of the three patients without relief of pain suggests a greater displacement of the CO_2 response curve to the left (respiratory stimulation) in patients whose pain was alleviated. However, the data are too few to be meaningful. The response curves of the one patient with complete relief of pain by placebo are also presented in figure 1.

Discussion

These data clearly indicate that meperidine, in doses which relieve acute postoperative pain, depresses respiration in a fashion qualitatively similar to that seen in healthy subjects. Since CO_2 response curves after small intravenous doses of meperidine have not been studied in healthy subjects, any quantitative similarity must be estimated from studies of intramuscular meperidine. Loeschcke *et al.*[9] who gave 150 mg. meperidine intramuscularly to healthy

Table 6. Displacement of Carbon Dioxide Response Curve by Placebo and Meperidine

(Displacement to the right is positive)

	No. of Patients	After Placebo (mm. Hg $Paco_2$)	No. of Patients	After Meperidine (mm. Hg $Paco_2$)
Abdominal operations	3	−0.40	6	3.58 ± 0.57†
Thoracic operations	2	−0.25	7	3.13 ± 1.11*
Total	5	−0.33 ± 0.34	13	3.36 ± 0.63†

* Significant drug effect at $P < 0.05$.
† Significant drug effect at $P < 0.01$.

subjects during breathing of air, observed a 10 per cent decrease in respiratory minute volume, a 15 per cent increase in respiratory rate, and an increase of 3.9 mm. Hg in end-tidal P_{CO_2}. The slope of the respiratory response curve decreased by 50 per cent, and by our estimate was displaced to the right 9–10 mm. Hg $P_{A_{CO_2}}$. Keats, Kurousu and Telford [10] studied the effects of 100 mg. meperidine administered intramuscularly to healthy subjects. During breathing of air, meperidine produced an insignificant change in respiratory rate, a 30 per cent decrease in respiratory minute volume and an increase in end-tidal P_{CO_2} of 5.3 mm. Hg. The displacement of the carbon dioxide response curve was estimated to be 8 mm. Hg $P_{A_{CO_2}}$ with a decrease in slope of approximately 50 per cent. Patients in the study reported here were given an average dose of meperidine of 28.5 mg., intravenously, representing 20–30 per cent of the intramuscular doses used in the studies cited. This dose produced a 10 per cent decrease in minute volume, a 10 per cent decrease in respiratory rate, an increase in $P_{A_{CO_2}}$ of 2.0 mm. Hg on breathing of air, and a 3.4 mm. Hg displacement of CO_2 response curve with a 20 per cent decrease in slope. A comparison of these doses and effects strongly suggests that respiratory depression by meperidine is at least as great in postoperative patients as in healthy subjects. It also suggests that studies in healthy subjects provide a good estimate of the respiratory depression to be expected from analgesics given for postoperative pain.

Many anesthesiologists have observed that the strong sensory input produced by the severe pain of a surgical incision or by rectal dilatation can lead to respiratory stimulation sufficient to overcome respiratory depression by narcotics and anesthetics. Such stimuli are, however, more akin to induced pain or experimental pain which is little modified by potent analgesics, in contrast to the response of noninduced or pathologic pain to such drugs.[11] Nevertheless, on the basis of such observations as these, it is conceivable that painful stimuli could antagonize the respiratory depressant actions of potent analgesics when pain is not relieved. It is also conceivable that the existence of naturally-occurring pain could stimulate respiration sufficiently so

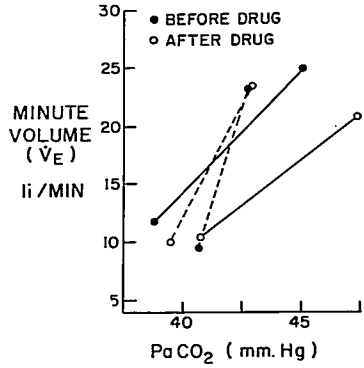

FIG. 1. CO_2 response curves before and after meperidine (solid line), plotted from mean data of 13 postoperative patients on the first postoperative day. Meperidine produced a 20 per cent decrease in slope and displaced the curve to the right by 3.4 mm. Hg. $P_{A_{CO_2}}$ (respiratory depression). The CO_2 response curves before and after placebo (broken line) for the one patient who obtained complete and sustained pain relief following a placebo are also shown. The post-drug curve is displaced slightly to the left, suggesting respiratory stimulation.

that relief of pain leads to apparent respiratory depression independent of any pharmacologic effect of the drug on the control of respiration.

Some of our data can apply to these questions. Since all our patients were given meperidine until pain was relieved, we are unable to determine if pain unrelieved would antagonize the respiratory depression of meperidine. However, in both patients in whom relief of pain was achieved by placebo the CO_2 response curve was displaced to the left (stimulation) 0.64 and 0.74 mm. Hg, rather than to the right (depression) as would be expected if pain were responsible for stimulating respiration. Some collateral evidence is also available from studies of the circulatory effects of narcotics given to patients with acute myocardial infarction. MacDonald *et al.*[12] gave 5 mg. heroin intravenously to eight patients, three of whom had pain at the time of study. Rees *et al.*[13] gave 100 mg. meperidine intravenously to eight similar patients,

two of whom had pain at the time of study. Respiratory depression, as measured by a decrease in Pa_{O_2} and an increase in Pa_{CO_2}, was approximately the same in patients with and without pain.

From these considerations it is difficult to ascribe any large role to pain, relieved or unrelieved, in the respiration of postoperative patients or in the modification of the pharmacologic effects of meperidine on the respiratory control mechanism. Except, perhaps, in extraordinary circumstances, respiratory depression should be expected to accompany analgesia by potent analgesics.

Some implications concerning the use of potent analgesics postoperatively are also suggested by these data. The use of narcotics has been considered a significant factor in the development of postoperative atelectasis,[14] possibly due to the elimination of normal intermittent depe breathing.[15] On the other hand, provision of relief of pain sufficient to permit deep breathing has also been considered important in preventing atelectasis. Therefore, unless regional analgesia is used to control postoperative pain, the use of potent analgesics postoperatively poses a therapeutic dilemma. The dilemma cannot be resolved by the use of small doses, since the desired effect is relief of pain and doses which relieve pain also depress respiration. The data presented here permit a different view of this problem.

Respiration of patients during pain was characterized by a rapid respiratory rate, a large minute volume of ventilation, normal Pa_{CO_2} and, from the few data which apply, Pa_{O_2} somewhat lower than expected. These data are strikingly similar to those reported by Diament and Palmer[16] and Palmer and Gardiner,[17] which were obtained on the first postoperative day following upper abdominal operations. In addition to higher respiratory rates and minute volumes compared with preoperative values, they observed lower vital capacity, lower forced expiratory volumes, lower expiratory reserve volumes and lower tidal volumes in patients after operation. A description of postoperative respiration is, therefore, not one of hypoventilation with hypercarbia, but rather one of the hyperventilation, predominantly an increased rate, with some abnormality of the ventilation–perfusion relationship to account for the low Pa_{O_2} values. This picture in patients with pain was little altered by relief of pain with narcotics. Significantly, Pa_{O_2} did not increase as a result of relief of pain, possibly because respiratory rate did not decrease. Whatever the reason, the general pattern of respiration was not altered and was not improved by relief of pain. Therefore, the respiratory characteristics responsible for postoperative atelectasis are not secondary to either pain or its relief but are characteristic of a systemic response induced by operation and present in the postoperative patient. Prevention of atelectasis, therefore, will depend on inducing patients to breathe deeply at frequent intervals with or without pain relief by potent analgesics. Clearly, this is more humanely and more effectively done by the patient when pain has been relieved adequately. Adjustments of dose, drug or route, of administration of postoperative analgesic drugs will not prevent postoperative atelectasis. Adequate relief of pain with properly-directed nursing care, however, will do so.

Of further interest in these data is the ease with which pain following major abdominal and thoracic operations was relieved by small intravenous doses of meperidine. In the usual treatment of postoperative pain, the physician estimates a uniform dose of analgesic to be given every three to four hours intramuscularly, as necessary, for the next 24 to 48 hours. Inherent in this practice of selecting a usual or average dose is the risk that some patients will still suffer pain and others will receive excessive doses, possibly with adverse reactions. The practice also ignores the fact that postoperative pain from the time of operation decreases in intensity.[18] It would seem more rational to treat an initial episode of postoperative pain by a small intravenous dose of analgesic in order to estimate the dose required for analgesia, and from this to estimate subsequent intramuscular doses which should then decrease for each 12-hour period after operation. Since most patients receive their initial doses of analgesic in a recovery room, this initial intravenous administration could be made conveniently, under close supervision. Untoward effects such as hypotension and respiratory depression would then be observed and treated. The wisdom of this recommendation is supported by the threefold range in doses required for analgesia in these patients

(15 to 40 mg.). An even wider range of analgesic requirements has been reported in patients who received postoperative analgesics intramuscularly.[18]

Addendum

Since submission of this manuscript, two papers which relate to the subject of this investigation have been published. W. H. Forrest and J. W. Bellville (Respiratory effects of alphaprodine in man, Obstet. Gynec. 31: 61, 1968) wrote: "It seems probable to us that the differences we observe between some studies (in healthy volunteers) and clinical experience are due to the nature of the population involved. Patients in pain respond differently from volunteers. Pain provides a physiologic stimulus so that respiratory depression is not as intense. The healthy young mother in labor and the good-risk postoperative patient might maintain good respiration under the stimulus of pain, even though receiving analgesic doses that would depress respiration in pain-free volunteers or in poor-risk postoperative or elderly patients." This speculation was not supported by our data.

Muneyuki *et al.* (Postoperative pain relief and respiratory function in man, ANESTHESIOLOGY 29: 304, 1968) compared the respiratory alterations produced by intravenous meperidine and by lumbar epidural analgesia when used to treat pain after upper abdominal operations. Patients were studied both on the day of and on the day after operation and were given somewhat higher doses of meperidine (43–55 mg./70 kg.) than those used in our study. Despite this, they observed little change in blood gases during breathing of air in most patients. The only significant change noted was a decrease in Pa_{O_2} in six subjects on the first postoperative day. The only consistently significant change following administration of meperidine was a decrease in minute volume of respiration. The usefulness of CO_2 response curves for detecting effects of narcotics on respiration was again affirmed. Differences in respiration resulting from the two methods for providing analgesia were surprisingly small considering the vastly different mechanisms involved.

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