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Physostigmine Antagonizes Morphine-induced Respiratory Depression in Human Subjects

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The effect of physostigmine on the respiratory depression induced by morphine was studied in human subjects who received morphine as part of their preanesthetic medication.

After pretreatment with droperidol (2.5–5 mg, iv) to prevent nausea, the change in minute ventilation was measured in 16 patients in response to increasing concentrations of inspired CO_2 (CO_2-response curve) by the rebreathing method. This was repeated 30 min after morphine (0.166 mg/kg, iv) in nine subjects and in seven controls who did not receive morphine and again 5–10 min after physostigmine (13–33 μg/kg, iv) in all subjects. All subjects were given N-butylhyoscine hydrobromide (5 mg, iv) to antagonize any peripheral cholinergic effects of physostigmine.

Morphine decreased the mean slope of the CO_2-response curve from 1.78 ± 0.18 to 1.12 ± 0.14 $l \cdot min^{-1} \cdot mmHg^{-1}$ ($P < 0.01$) and increased the alveolar P_{CO_2} for a fixed minute ventilation (position of curve) from 45.0 ± 1.3 to 51.9 ± 1.5 mmHg ($P < 0.001$). Physostigmine restored the mean slope after morphine to control value, *i.e.*, 1.79 ± 0.23 $l \cdot min^{-1} \cdot mmHg^{-1}$, and position to 46.2 ± 1.2 mmHg ($P < 0.001$). Physostigmine did not increase the slope or alter the position of the CO_2-response curves of subjects given droperidol alone.

The authors conclude that physostigmine can reverse the respiratory depressant effect of morphine and restore the sensitivity of the respiratory center of CO_2, presumably by raising acetylcholine levels in the brain after these have been reduced by morphine. (Key words: Analgesics: morphine. Antagonists: miscellaneous: physostigmine. Ventilation: carbon dioxide response.)

NARCOTIC ANALGESIC DRUGS depress respiration predominantly by reducing the sensitivity of brain-stem respiratory centers to carbon dioxide.[1] These drugs also inhibit the release of acetylcholine from neurons in the central nervous system.[2] On the other hand, application of acetylcholine to the floor of the fourth ventricle stimulates respiration,[3] while hypercarbia increases the release of acetylcholine in the brain stem.[4] Taken together, these findings suggest the possibility that morphinelike drugs diminish the sensitivity to CO_2 by reducing the amounts of acetylcholine in the area of the respiratory center that can be released in response to hypercarbia.

Weinstock *et al.* demonstrated that physostigmine, an anticholinesterase agent that raises the levels of acetylcholine in the brain, can antagonize the respiratory depressant effect of morphine in experimental animals.[5] The purpose of the present study was to extend these observations to the human subject by determining whether physostigmine restores the sensitivity of the respiratory center to carbon dioxide, and hence respiratory activity to normal values, after these have been depressed by morphine.

Materials and Methods

Approval by the Ethics Committee was obtained for this project, which was carried out in the Anesthetics Department of Hadassah Hospital, Jerusalem. Its purpose was explained to each patient, and informed consent was obtained. The 16 patients, 10 men and six women, were all between 17 and 50 years of age, free of pain, and without any clinical evidence of respiratory, cardiovascular, kidney, or liver disease.

The study was performed in the anesthetic induction room, and the droperidol and morphine that were administered constituted an integral part of the anesthetic premedication. Muscle relaxants were not employed in the subsequent operations.

EXPERIMENTAL PROTOCOL

All patients were premedicated with droperidol (5 mg, iv) before this study began. This drug was given, because in a pilot study we found that a number of patients complained of nausea and vomiting when given morphine and physostigmine and when subjected to hypercarbia. Droperidol was chosen in preference to a phenothiazine because it has only weak anticholinergic activity.[6]

The control response to CO_2 was measured once in all patients 10–15 min after droperidol. Preliminary studies had shown that in subjects sedated with droperidol, the slopes of control CO_2-response curves repeated at 15-min intervals for 45 min did not differ by more than 8%, and their position was reproducible to ±7%. It also was found that the maximum respiratory depressant effect of morphine was attained in most patients 20–40 min after intravenous injection, and this remained fairly constant for 30 min more. Nine patients (experimental group) were given morphine (0.166 mg/

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TABLE 1.

	Experimental Group (n = 9)		Control Group (n = 7)	
	Slope ± SE ($l \cdot min^{-1} \cdot mmHg^{-1}$)	Alveolar P_{CO_2} for Fixed Minute Ventilation ± SE (mmHg)	Slope ± SE ($l \cdot min^{-1} \cdot mmHg^{-1}$)	Alveolar P_{CO_2} for Fixed Minute Ventilation ± SE (mmHg)
Control, droperidol, 0.08 $mg \cdot kg^{-1}$, 10 min	1.78 ± 0.18	45.0 ± 1.3	1.53 ± 0.23	48.9 ± 0.7
Morphine, 0.166 $mg \cdot kg^{-1}$, 30 min or droperidol 0.08 $mg \cdot kg^{-1}$, 40 min	1.12* ± 0.14	51.9† ± 1.5	1.75 ± 0.16	47.6 ± 1.1
Physostigmine‡, 5–10 min	1.79§ ± 0.23	46.2¶ ± 1.2	1.38** ± 0.12	48.6 ± 0.8

* Significantly different from control, $P < 0.01$.
† Significantly different from morphine, $P < 0.01$.
‡ Mean concentration for experimental group, 18.7 ± 1.9 $\mu g \cdot kg^{-1}$ (range 13–33 $\mu g \cdot kg^{-1}$); Mean concentration for control group, 18.2 ± 0.8 $\mu g \cdot kg^{-1}$ (range, 16–22 $\mu g \cdot kg^{-1}$)
§ Significantly different from control $P < 0.001$.
¶ Significantly different from Morphine $P < 0.001$.
** Significantly different from droperidol $P < 0.05$.

kg) by slow intravenous infusion during 5 min and seven others (control group) were given saline. Their responses to CO_2 were assessed 30 min later. Buscopan (N-butyl hyoscine hydrobromide) 5 mg was injected to prevent any peripheral cholinergic effects of physostigmine, followed 5 min later by physotigmine (1–2 mg) infused during 5 min. The CO_2-response curve was repeated 5–10 min after the end of the physostigmine infusion and again in six of the patients of the experimental group 30–40 min after physostigmine. Blood pressure and heart rate were measured throughout the study at 10-min intervals.

Measurement of the Response to CO_2

The response to CO_2 was assessed by the rebreathing technique of Read,[7] in which the subjects inhaled a mixture of 5% CO_2 and 95% O_2 initially in a closed system. In both methods, the percentage of CO_2 in the expired air was monitored continuously on a Godart–Statham capnograph. From these values, the appropriate alveolar P_{CO_2} was computed. Minute ventilation was calculated from the respiration rate and tidal volume, which also were monitored continuously on a Collins 9-l spirometer.

The CO_2-response curves were constructed for each patient before and after the various drug treatments from values of minute ventilation and alveolar P_{CO_2} as described by Read *et al.*[7] Only the points on the linear portion of the graph close to the midpoint were used for the calculation of the slope of the relationship by the method of least squares. The position of the CO_2-response curve is defined most accurately at the midpoint of the data. The minute ventilation at this point varies for different patients but remains constant for a given patient after various drug treatments.[8] An appropriate fixed value of 5, 10, or 15 l/min^{-1} was chosen from the midpoint of the control graph of each patient and used to determine the alveolar P_{CO_2} before and after the drug treatments. This value was used to define the position of the CO_2-response curve and to compare the ventilation response with the response to administered drugs, irrespective of whether or not there was a change in its slope.

Statistical Analysis

Data were analyzed by a one-way analysis of variance for repeated measures.[9] Post hoc individual group comparisons were performed with the Neuman–Keul's test.[9]

Results

The minute ventilation closest to the midpoint of the control curve that was chosen for the determination of the position (alveolar P_{CO_2}) of the CO_2-response curve in 16 subjects was 5 l/min in two, 10 l/min in seven, and 15 l/min in seven subjects.

The dose of morphine (0.166 mg/kg) given caused evidence of respiratory depression, as indicated by a significant shift in the position of the CO_2-response curve to the higher value of PA_{CO_2} and a decrease in its slope. Physostigmine restored the position and slopes of the CO_2-response curves to their premorphine values (table 1). The effects of morphine and physostigmine on the slope of the CO_2 response curves were significant ($F = 10$, $df = 2/16$, $P < 0.01$), as were those on the position of the CO_2-response curves ($F = 27.4$, $df\ 2/16$, $P < 0.001$).

A significant correlation ($P < 0.05$) was found between the reduction in alveolar P_{CO_2}, increase in slope, and the dose (in $\mu g/kg$) of physostigmine (fig. 1*A* and *B*). Doses in the range of 16–20 $\mu g/kg$ appeared to be sufficient to antagonize the respiratory depressant effect of morphine, 0.166 mg/kg.

In six patients, the CO_2-response curve also was determined 30–40 min after physostigmine. The alveolar P_{CO_2} increased significantly ($P < 0.05$ $F = 9.3$, $df = 3/15$), and the slope decreased in two of the patients, indicating that the effect of physostigmine was beginning to wear off.

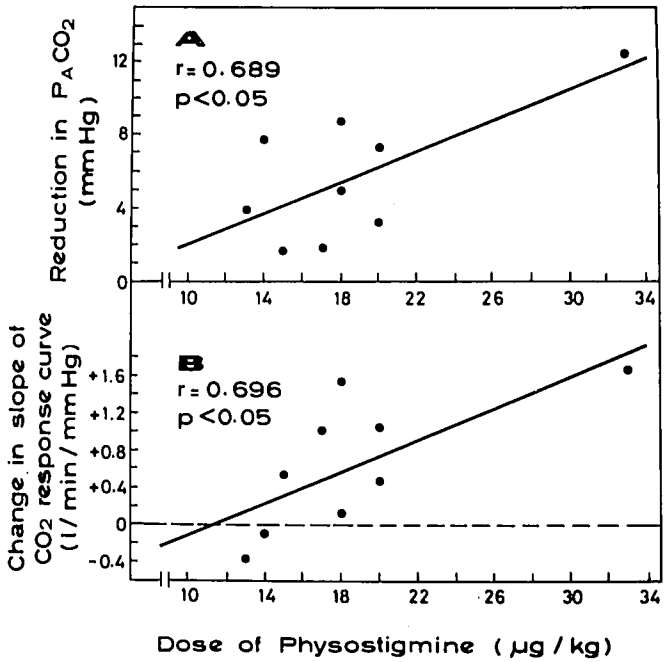

FIG. 1. The relationship between the change in slope of the CO_2-response curve and its position and the dose of physostigmine administered.

To determine whether the change in minute ventilation induced by physostigmine was caused by antagonism of morphine-induced respiratory depression or resulted from a general analeptic effect, physostigmine also was given to a group of seven patients that had only received droperidol. A pilot study in nine patients had shown that droperidol (5 mg) alone did not significantly alter either the slope or position of the CO_2-response curve from the predrug level. The control values for slope and alveolar P_{CO_2} were 1.82 ± 0.16 $l \cdot min^{-1} \cdot mmHg^{-1}$ and 50.0 ± 1.5 mmHg, and after droperidol, 1.76 ± 0.17 $l \cdot min^{-1} \cdot mmHg^{-1}$ and 49.1 ± 0.5 mmHg, respectively. Physostigmine given in a dose range that significantly increased minute ventilation after morphine (16–22 μg/kg) did not alter the alveolar P_{CO_2} but caused a significant decrease in the slope of the CO_2 response curve after droperidol ($F = 4$, $df = 2/12$ $P < 0.05$). It was noted that physostigmine lowered the threshold PA_{CO_2} from 42.3 ± 0.8 mmHg to 39.8 ± 1.0 mmHg and raised the minute ventilation at this level of PA_{CO_2} from 9.3 ± 1.0 to 11.4 ± 1.0 l/min. Thus, while there appeared to be some stimulation of respiration at low levels of inspired CO_2, as the latter increased, the stimulant effect of physostigmine declined.

Buscopan caused only a transient increase in mean heart rate, from 76 ± 3 to 84 ± 4 min^{-1}. The pupils remained constricted after morphine, even when buscopan was given. None of the patients complained of peripheral cholinergic side effects after physostigmine such as sweating, hypotension, bradycardia, or abdominal cramps, indicating that these had been controlled successfully by buscopan.

Discussion

Determination of the change in response to inhaled CO_2 is a widely used test for depression of respiratory function and can show an altered response even before there is any detectable change in arterial blood P_{CO_2}. The slope of the response curve is an index of the "gain" of the system, and its position has been described as the "detector."[10] In our study, the latter was found to be a more sensitive measure of narcotic depression.

Morphine (0.166 mg/kg, iv) produced a significant suppression of resting ventilation in all nine pain-free subjects, as indicated by a shift to the right of the CO_2-response curve. Furthermore, in eight of the subjects, the slope of the relationship between alveolar P_{CO_2} and minute ventilation also was reduced by more than 30%. This clearly indicated that morphine had decreased the sensitivity of the respiratory center to CO_2.

Physostigmine (13–33 μg/kg) restored the resting ventilation to premorphine values in eight out of nine patients within 5–10 min of its injection. It also increased the slopes of the CO_2-response curves to the control value. There was a significant correlation between the increase in slope produced by physostigmine of the CO_2-response curves ($r = 0.70$, $P < 0.05$), in its position ($r = 0.69$, $P < 0.05$) in morphine-treated subjects, and in the dose of physotigmine administered. The action of physostigmine lasted 35–45 min. This is in accordance with the known short half-life of this drug.[11] and with previous findings in which physostigmine has been used to antagonize effects of antidepressant drugs[12] and fentanyl.[13] The present findings clearly show that physostigmine rapidly can reverse the respiratory depressant effect of morphine and restore the sensitivity of the respiratory center to CO_2.

Activation of central cholinergic receptors results in a stimulation of respiration with a fall in Pa_{CO_2} and rise in Pa_{O_2}.[14] Hypercarbia, which also stimulates respiration, has been shown to increase the release of acetylcholine from medullary neurons in experimental animals.[4] Conversely, morphine inhibits acetylcholine release[2] and suppresses the sensitivity of the respiratory center to CO_2.[1] Physostigmine increases the level of acetylcholine in the brain by inhibiting its hydrolysis. In this way, more acetylcholine becomes available for interaction with receptors subserving respiratory control and the respiratory depressant effect of morphine can be overcome. Since physostigmine did not cause any increase in the ventilatory response to CO_2 in subjects given droperidol alone, it is likely that this antagonism of morphine-induced depression results from a resto-

ration of normal acetylcholine levels rather than from a nonspecific analeptic effect.

While low doses of physostigmine appears to be able to stimulate respiration in animals breathing air[15] or in human subjects when inspired CO_2 is relatively low, it does not appear to be able to do so when higher levels of $P_{A_{CO_2}}$ are reached. Thus, the slope of the CO_2-response curve in these subjects is lower than in controls. Larger doses of anticholinesterase drugs are known to depress respiration because of excess accumulation of acetylcholine in the central nervous system (CNS).[16] Because hypercapnia increases the release of acetylcholine in the medulla,[4] it is possible that the combined effects of an anticholinesterase and high $P_{a_{CO_2}}$ result in a level of acetylcholine in the vicinity of the respiratory center that is high enough to depress respiration.

Physostigmine does not antagonize the analgesic activity of opiates in experimental animals[17] or in postoperative human subjects.[18] Furthermore, it has been shown to elevate pain threshold in experimental pain in human subjects.[19] If physostigmine clearly overcomes respiratory depression without antagonizing the analgesic effect of opiates in clinical pain, it should be useful in postoperative pain management and perhaps superior to the narcotic antagonists.

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