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Effects of Droperidol on Respiratory Drive in Humans

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The sensitivity of the respiratory center following a single 0.3 $mg \cdot kg^{-1}$ iv dose of droperidol was determined in eight healthy volunteers by using carbon dioxide (CO_2) rebreathing and mouth occlusion pressure measurements ($P_{0.1}$). There were no significant differences in the mean slopes of the minute ventilation/partial pressure of CO_2 ($\dot{V}_E/P_{CO_2}$) and log $P_{0.1}/P_{CO_2}$ relationships between control measurements and those made 30, 60, 90, 150, and 240 min after droperidol administration. However, individual variations in response were present, one subject showing significant (approximately 50%) depression of respiratory drive. (Key words: Hypnotics: butyrophenones, droperidol. Carbon dioxide: ventilatory response. Ventilation: mouth occlusion pressure; carbon dioxide response.)

DROPERIDOL, a butyrophenone derivative, is used widely in anesthetic and other medical practices, but there are only a few reports about its respiratory effects. It has been reported that droperidol causes small decreases in tidal volume, minute ventilation, functional residual capacity (FRC), and airway resistance,[1,2] however, these measurements are inadequate to determine the effects of the drug on respiratory drive. This can be assessed by determining the ventilatory response to CO_2 rebreathing and by mouth occlusion pressure measurements. These evaluations were made in this study.

Materials and Methods

The study was conducted in eight ASA class I volunteers of either sex (two women and six men) who gave written informed consent in accordance with a protocol approved by the Hospital Ethics Committee. The mean age of the subjects was 29.9 ± 5.0 (SD) yr, and their mean weight was 68.8 ± 12.4 kg. None were being treated with medication, and all had fasted overnight.

Respiratory center sensitivity to CO_2 was determined using a modified Read rebreathing method (fig. 1).[3] Each subject was studied in a 30° head-up position, with a nose clip in place and connected by means of a rubber mouth piece to a closed-circuit, 6-l bag in box system, initially filled with a 3% CO_2-50% O_2-47% nitrogen gas mixture. Mouth occlusion pressure in cm H_2O, 100 ms after the onset of inspiration ($P_{0.1}$), was measured using an occlusion device similar to the one described by Delavault and Saumon[4] and a Statham PM5 differential transducer. The resistances of the inspiratory and expiratory lines with the occlusion device in the open position at a flow rate of 5 $l \cdot s^{-1}$ were 4.5 and 2.7 cm $H_2O \cdot l^{-1} \cdot s$, respectively; subjects did not seem to perceive this slight increase in resistance. Seven to 10 transient occlusions were triggered randomly by the investigator at 20–40 s intervals when CO_2 concentration was in the 7.0–9.5% range. A remote control device was used so that subjects were unaware when these would occur. Air flow was measured in the bag in box, using a Fleisch pneumotachograph, model 2, and a Hewlett-Packard differential transducer, model 270, from which minute ventilation ($\dot{V}_E$) was derived by electronic integration of the last three breaths preceeding each occlusion. Calibration was performed with a one-liter Hamilton syringe. CO_2 fraction was measured in the bag in box with a Siemens Ultramat M-CO_2 infrared analyzer calibrated with an Associated Electrical Industries, (London), MS4, mass spectrometer before and after the experiment. In previous studies, we verified that above 7% CO_2, the P_{CO_2} in the bag was virtually identical to end-tidal P_{CO_2} (unpublished data). Measurements were performed in the CO_2 range of 7.0–9.5% and required 5–7 min; $P_{0.1}$, $\dot{V}_E$ and P_{CO_2} were recorded simultaneously (paper speed, 5 $mm \cdot s^{-1}$). Additional pulmonary function tests, *i.e.*, lung volumes and forced expiratory volume (FEV_1) and FRC were measured using standard methods (functional residual capacity was measured using helium dilution).[5] Values were converted to body temperature and pressure saturated with water vapor (BTPS).

The course of events throughout the experimental day was as follows. Each subject arrived at 8:00 AM and rested for 1 hr, during which time a cannula was inserted in a large vein of the forearm. Normal saline with 5% glucose was infused at a rate of approximately 100

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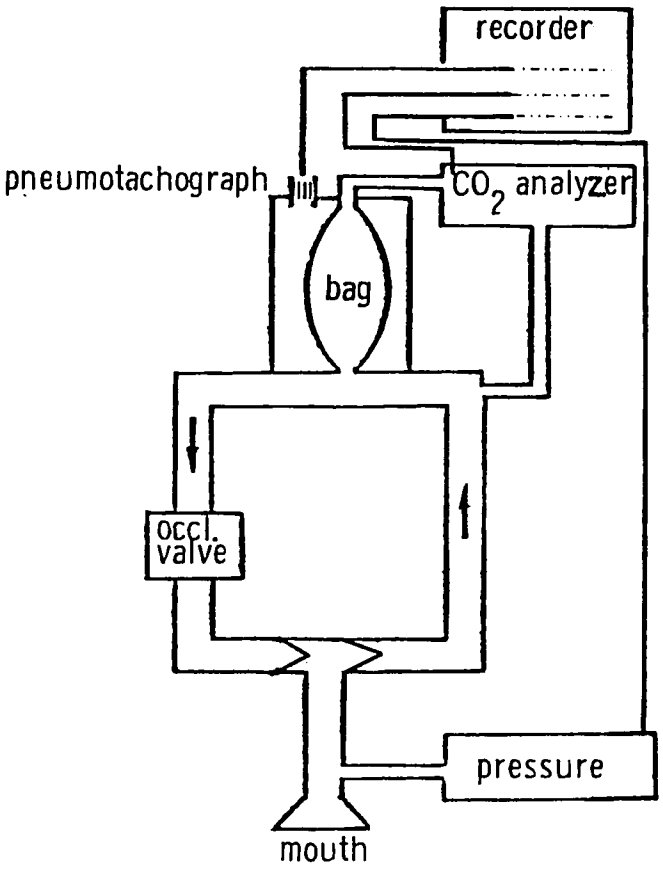

FIG. 1. General arrangement of the circuit.

$ml \cdot h^{-1}$ through this channel. During the tests, great care was taken to ensure that subjects were comfortable and undisturbed. To begin the study, two CO_2 rebreathing control tests were made, but only the second was used, because the first was considered a practice run. Droperidol, 0.3 $mg \cdot kg^{-1}$, then was infused over a 3-min period through the cannula. Additional measurements were performed 30, 60, 90, 150, and 240 min after droperidol injection. Functional residual capacity was measured before and 15 min after droperidol administration.

Regression lines for each time interval for each subject were drawn by the least squares method to fit the set of points log $P_{0.1}$ *versus* P_{CO_2}, and $\dot{V}_E$ *versus* P_{CO_2} in the 7.0–9.5% CO_2 range. Logarithmic transformations of the data were used because the relationship of P_{CO_2} and $P_{0.1}$ were alinear in some subjects. Mean values (±SD) of the slopes for each time interval were calculated and compared with control period data using repeated measure analysis of variance.[6] Also, in each subject, an individual comparison between each time interval following droperidol injection and the control period was performed first by comparing the slopes of the regression lines by analysis of variance and then by applying the Bonferroni multiple comparison procedure.[6]

Results

Results of the measurements of lung volumes, FEV_1 and FRC, are presented in table 1. All values were within normal limits. FRC after drug administration was 97.5 ± 6% of control value, indicating that experimental conditions were the same before and after droperidol injection.

There were no significant differences in the mean slopes of the $\dot{V}_E/P_{CO_2}$ and log $P_{0.1}/P_{CO_2}$ relationships at any time interval (table 2). The F values of $\dot{V}_E/P_{CO_2}$ and log $P_{0.1}/P_{CO_2}$ were, respectively, 0.4 and 1.4. Nontransformed $P_{0.1}/P_{CO_2}$ data also were analyzed with the same result. Examination of individual data, however, showed a wide range of responses among the subjects (tables 3 and 4). Subject FR consistently showed approximately 50% depression of $P_{0.1}$. Occasional depression of $\dot{V}_E$ was observed in subjects, PP, FB, and PL, while a stimulant effect in $\dot{V}_E$ was observed in subjects PG and FP.

The study was not designed to evaluate side effects, however, several were observed. Two subjects (ED and

TABLE 1. Details of Subjects Studied

Subject	Age (yr)	Weight (kg)	Height (cm)	VC* (ml)	$\frac{FEV_1}{VC}$† (%)	FRC‡ before Droperidol (ml)	FRC 15 minutes after Droperidol (ml)	Change in FRC (%)
PP	32	72	180	7,180	77.6	2,970	3,050	+2.7
FR	26	66	181	5,860	80.1	2,550	2,570	+0.8
ED	27	78	190	6,160	86.3	2,900	2,810	−3.1
PG	38	80	176	5,370	82.2	2,450	2,530	+3.3
FP	35	84	178	4,270	82.5	—	—	—
FB	23	64	178	5,100	80.0	2,170	2,070	−4.6
PL	31	58	174	4,590	80.2	2,350	2,020	−14.0
MD	27	48	158	3,600	80.7	—	—	—

* VC = vital capacity.
† FEV_1 = forced expiratory volume in $1 \cdot s^1$.
‡ FRC = functional residual capacity.

TABLE 2. Mean* (±SD) Slopes of log $P_{0.1}/P_{CO_2}$ and $\dot{V}_E/P_{CO_2}$ before (Control) and after Droperidol Administration

	Slope $\frac{\log P_{0.1}}{P_{CO_2}}$	Slope $\frac{\dot{V}_E}{P_{CO_2}}$
Control	0.072 ± 0.027	1.02 ± 0.60
30 min after	0.056 ± 0.026	0.87 ± 0.57
60 min after	0.068 ± 0.032	0.94 ± 0.56
90 min after	0.062 ± 0.025	0.90 ± 0.46
150 min after	0.063 ± 0.022	0.98 ± 0.54
240 min after	0.058 ± 0.020	0.82 ± 0.52

* n = 8.

FR) experienced anxiety during the experiment, and one subject (FP) had transient (2 min) masseter muscle spasm immediately after droperidol was injected. One subject (FR) had paralumbar muscular spasms 240 min after receiving droperidol and could not perform the occlusion test at that time.

Discussion

The response to CO_2 rebreathing is one of the most sensitive measurements of the effect of a drug on respiration. In recent years, an additional refinement, *i.e.*, measurement of mouth occlusion pressure, has been added to the determination of CO_2 response curves.[3] Occlusion pressure developed in the first 0.1 s after the onset of inspiration ($P_{0.1}$) is of value in assessing both the neuronal drive to the respiratory muscles and the effectiveness of inspiratory muscle contraction in producing pressure, without being affected by flow resistance and compliance of the respiratory system, or by vagal volume-related reflexes. Thus, the occlusion pressure response to CO_2 clearly reflects the responsiveness of the respiratory centers to CO_2.[7,8] Until the present study, the respiratory effects of droperidol have not been examined using this technique.

In our study, no consistent pattern of respiratory effects emerged. Changes in the mean values of the slopes of the $\dot{V}_E/P_{CO_2}$ and log $P_{0.1}/P_{CO_2}$ curves after droperidol administration did not differ from control values. These results occurred despite the fact that we administered a relatively large dose of droperidol, 0.3 mg·kg^{-1} iv, to emphasize any potential effects the drug might have. The absence of changes in mean values might suggest that droperidol is devoid of significant effects on the respiratory center. However, some volunteers demonstrated evidence of significant stimulation or depression of respiration in response to hypercapnia. This seeming discrepancy, in part, could result from the variable incidence and nature of drowsiness and of side effects, such as anxiety and dyskinesia, that were observed during the experiment. However, all subjects experienced some degree of drowsiness, and

TABLE 3. Individual Slopes of $\dot{V}_E P_{CO_2}$ (l·min^{-1}·mmHg^{-1})

	Control	Minutes after Droperidol Administration				
		30	60	90	150	240
FR	1.53	0.93	0.89	0.83	1.41	—
PP	1.54	0.27*	1.27	0.77	0.95	0.84
ED	1.79	1.74	1.64	1.48	1.75	1.75
PG	0.27	0.81*	0.41	0.74	0.48	0.34
PL	0.68	0.26*	0.33	0.46	0.52	0.49
MD	0.47	0.32	0.34	0.27	0.25	0.33
FP	0.47	1.15	0.93	1.11*	1.00*	1.24*
FB	1.40	1.51	1.68	1.55	1.48	0.78*

* Significant variations from control values ($P < 0.05$).

those subjects having side effects did not form a subgroup with a consistent pattern of responses. Thus, this explanation does not seem likely, and we conclude that a single, 0.3 mg·kg,$^{-1}$ iv dose of droperidol does not have a consistent depressant effect on respiratory drive, although individual subjects may show variable and, at times, marked changes. This pattern of variability probably represents the normal biologic distribution of responses to a potent drug that does not have specific effects on respiratory drive.

Other studies have not examined the effects of droperidol alone on respiratory drive, although some ventilatory measurements have been made. Cottrell *et al.*,[2] using 0.07 mg·kg^{-1} of droperidol im for premedication, reported a moderate decrease in FRC and in airway resistance. Soroker *et al.*,[1] using a dose of 5 mg im for premedication in adults, observed a slight but significant decrease in $\dot{V}_E$, owing to a change in tidal volume (V_T) without a change in respiratory rate. In another study, Harper *et al.*[9] examined the effects of iv administration of fentanyl alone and of the combinations of approximately 0.2 and 0.4 mg of fentanyl with 10 and 20 mg of droperidol, respectively, on the ventilatory response to CO_2 breathing in volunteers. The addition of droperidol to fentanyl did not increase or prolong further the respiratory depression seen with

TABLE 4. Individual slopes of log $P_{0.1}/P_{CO_2}$

	Control	Minutes after Droperidol Administration				
		30	60	90	150	240
FR	0.112	0.052*	0.071*	0.056*	0.081*	—
PP	0.071	0.084	0.092	0.085	0.065	0.069
ED	0.099	0.082	0.093	0.073*	0.088	0.087
PG	0.026	0.030	0.017	0.022	0.019	0.022
PL	0.065	0.034	0.036	0.060	0.048	0.061
MD	0.066	0.056	0.092	0.058	0.053	0.052
FP	0.053	0.026	0.040	0.039	0.069	0.047
FB	0.081	0.086	0.100	0.103	0.078	0.066

* Significant variations from control values ($P < 0.05$).

fentanyl alone at equivalent doses. Moreover, Becker *et al.*[10] showed that droperidol did not enhance the respiratory depression produced by fentanyl but may attenuate it, in fact. These data are insufficient to establish the nature and the magnitude of the effects of droperidol on respiratory drive. Similarly, measurements of lung volumes, $\dot{V}_E$ and airway resistance after administration of other premedicant drugs have led to the erroneous conclusion that these agents do not cause respiratory depression.[1,11,12] When mouth occlusion pressure measurements were made, however, depression of respiratory center activity was found. In the case of diazepam, for example, as much as 50% depression has been detected.[13,14] The value of such information to anesthetists is obvious.

The clinical implications of this study are that droperidol, when administered alone to healthy subjects, even in large doses, generally is devoid of significant respiratory depressant effects. However, depression may occur in some individuals. Thus, if large doses are administered, particularly to patients who have received respiratory depressant drugs or in whom respiration is otherwise embarrassed, it may be appropriate for one to carefully monitor respiration.

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