Respiratory Depression in the Sedated Bronchitic Patient:

Rapid Version of the CO_2 Response Curve

Martin I. Gold, M.D., Stanley Reichenberg, M.B., M.R.C.P., Eric Freeman, M.D.*

The $P\bar{v}_{CO_2}$, FEV_1/VC and CO_2 response curves of nine bronchitic patients with severe airway obstruction were measured. Pentobarbital, 100 mg, and a placebo were ingested on two separate days, in random order. The barbiturate did not alter the ventilation P_{CO_2} response curve significantly. Changes in $P\bar{v}_{CO_2}$ and FEV_1/VC were minimal and were similar on both days. Five patients became extremely drowsy or fell asleep with the barbiturate but not with the placebo; this central nervous system depression was out of proportion to the dose; two patients went into respiratory failure. The authors believe measurements of the ventilation P_{CO_2} respiratory curve are of limited value in assessing drug-induced respiratory depression in such patients. Furthermore, this relatively low dose of barbiturate may initiate serious complications.

HALDANE'S observations in 1892 still serve as the basic framework within which carbon dioxide response represents a working index of respiratory depression or stimulation[4] The carbon dioxide–ventilation response curve is a practical method for studying the actions of drugs on respiration, since the relationship between ventilation and changes in P_{CO_2} is linear.[1–5] Recently the nonsteady-state technique has been modified such that the patient inhales from a bag containing a mixture of carbon dioxide approximately equal to his mixed venous CO_2 ($P\bar{v}_{CO_2}$).[1,2] The time required to perform the test thus is decreased to approximately four minutes. The technique involves rapid development of equilibrium between bag, lung and blood, the end-tidal carbon dioxide (P_{ETCO_2}) rapidly equalling the $P\bar{v}_{CO_2}$ and, eventually, tissue P_{CO_2}.[2,3]

The present study involved patients with severe bronchitis and chronic airway obstruction with elevated $P\bar{v}_{CO_2}$ values, who recently had recovered from acute respiratory failure. They were given 100 mg pentobarbital (Nembutal) in an attempt to see if their already slope-depressed CO_2 response curves would be depressed further.[7] Slope (s) and intercept (B) describe volume–P_{CO_2} changes in an idealized fashion; the latter two variables plotted in an X–Y manner were used in the investigation.[5]

Materials and Methods

Nine patients who had had known chronic airway obstruction for at least five years and six normal volunteers were studied. Each patient had a forced expiratory volume, one second (FEV_1) of 1 l or less, persistent cough and expectoration. All had increases in $P\bar{v}_{CO_2}$ of approximately 10–30 mm Hg above accepted normal values. All clearly understood the purpose and risks of this study and provided informed consent to receive either 100 mg of pentobarbital or a placebo in random fashion on two separate days, interrupted by at least one day of rest. A CO_2 response test was performed the day prior to the planned investigation to serve as a baseline and to familiarize the patient with the procedure.

A control $P\bar{v}_{CO_2}$, FEV_1/VC (forced expiratory volume, 1 second/vital capacity) and CO_2 response curve were obtained. The capsule containing either placebo or drug was then administered orally in a coded planet according to accepted double-blind techniques. Measurements were repeated at 45, 90 and 135 minutes. The $P\bar{v}_{CO_2}$ was measured using the plateau technique.[8] After a three-minute rest followed by a deep expiration, the sitting patient inhaled gas from a bag-in-a-bottle system to initiate the CO_2 response test. (Fig. 1). The eight-liter bag contained 2–4 l,

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according to the Patient's FEV_1, of approximately 7 per cent CO_2 and 93 per cent O_2. This was adjusted to within ±15 mm Hg of the patient's $P\bar{v}_{CO_2}$. In addition, instrumentation included a 10-l calibrated Parkinson Cowan dry gas meter fitted with a potentiometer, the output of which was recorded on a Mingograph 81 or SS. P_{ETCO_2} was measured by an infrared analyzer (Godart Capnograph, CPI); this was calibrated with gas mixtures containing CO_2 and O_2 whose concentrations had been measured by Lloyd's modification of a Haldane apparatus. Gas mixtures used were 3, 5, 9 and 12 per cent CO_2. The oxygen concentration in the rebreathing bag was measured by a paramagnetic oxygen analyzer, Servomex type OA-150. Since the oxygen concentration was above that in air, a correction for collision broadening was made and gas volumes were converted to BTPS. A dry spirometer with a battery-operated transistor timer was utilized to measure FEV_1/VC.[9]

The paper trace was run continuously at a speed of 25 mm/sec for an average of four minutes per CO_2 response curve. After the initial 30 seconds needed to reach equilibrium, gas and volume points from end-expiration to end-expiration were chosen every 30 to 45 seconds. The average P_{ETCO_2} and minute volume ($\dot{V}_E$) representing each of the time sequences were calculated as in figures 2 and 3. These gas and volume data were submitted to an Elliot 4100 computer programmed for the solution of the following linear regression equation by the method of least squares:

$$\dot{V}_E = s_{CO_2}(P_{CO_2} - B_{CO_2})$$

Here, $\dot{V}_E$ equals minute volume, s_{CO_2} equals slope of the CO_2 response curve, P_{CO_2} equals carbon dioxide tension and B_{CO_2} equals intercept of this CO_2 response curve. With rare exceptions all s data had correlation coefficients (R) of 0.85 or greater. The results obtained on the drug day and the placebo day and their corresponding control values were submitted to statistical analysis by Students *t* test for significance at the 5 per cent level. All s data were analyzed for drug result and control, and placebo result and control at the three times after ingestion.

Results

Table 1 shows the results derived from six normal volunteers with a mean control s of

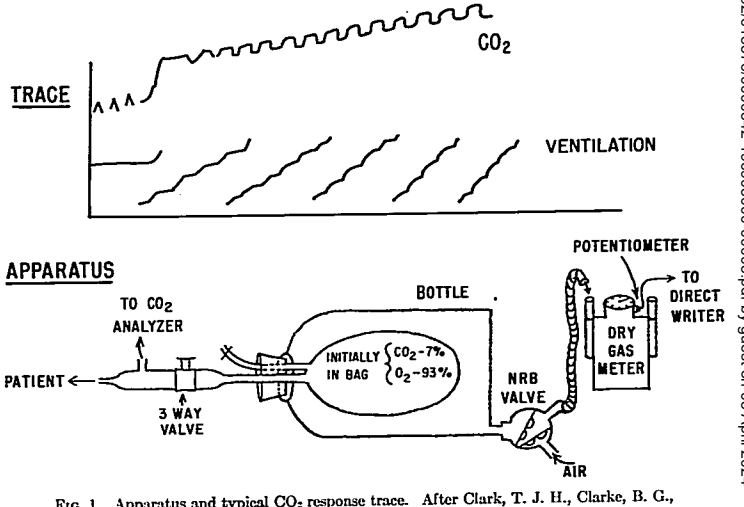

FIG. 1. Apparatus and typical CO_2 response trace. After Clark, T. J. H., Clarke, B. G., and Hughes, J. M. B.[10]

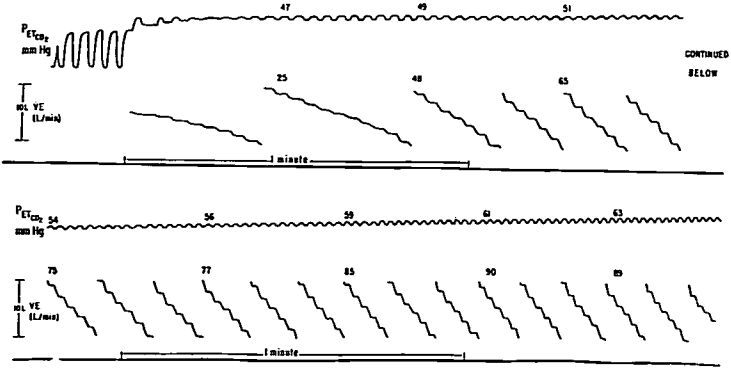

FIG. 2. CO_2 response curve in a normal volunteer.

3.5 l/min/mm Hg. A simulated test situation without drugs was instituted with CO_2 response curves at 45, 90 and 135 minutes after the "control" curve. The coefficient of variation of s for each volunteer was 11 per cent.

In table 2 the s and B data from nine bronchitic patients are shown. Figure 4 is a bar graph expressing these data changes as per cent deviation from control. Patients 1, 2, 3, 6 and 7 showed greater s depression on the day pentobarbital was given. In patients 5 and 9, s was depressed on both test days, but more on barbiturate day. Patients 4 and 8 exhibited more depression with the placebo than with the drug. The mean barbiturate s data at 45, 90 and 135 minutes and corresponding control were compared with placebo and control ($P > 0.05$).

Figures 2 and 3 depict typical CO_2 response curves illustrating $\dot{V}_E$ and $P_{ET_{CO_2}}$ parameters in a normal volunteer and a bronchitic patient. Note the initially high $P_{ET_{CO_2}}$ in the bronchitic patient and the lack of stimulation of $\dot{V}_E$.

Table 3 presents morphologic data from the

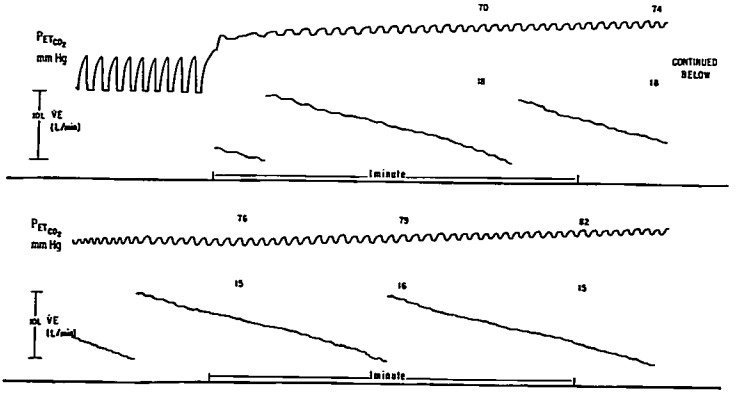

FIG. 3. CO_2 response curve in a bronchitic patient.

patients. Central nervous system depression occurred in patients 1, 3, 4, 5 and 6 on the barbiturate day, and in patient 1, prolonged drowsiness occurred, gradually clearing during the succeeding 48 hours. Patients 3 and 6, both of whom showed depression of the CO_2 response curve, developed exacerbation of respiratory failure with delayed rises in $P\bar{v}_{CO_2}$ 10 mm Hg above control values. They required intensive conservative management with controlled oxygen therapy.[15] The severe reaction in patient 3 may have been accounted for by coexisting hepatic cirrhosis, although the individual was vigorous in appearance and patient 6 initially showed the highest degree of respiratory failure in the group.

The $P\bar{v}_{CO_2}$ and spirometry data are shown in table 4. Mean $P\bar{v}_{CO_2}$ was 64 mm Hg before either drug was administered, while mean FEV_1/VC was 0.7/1.9. There was little difference between values for each patient on the placebo or barbiturate day and the mean ($P > 0.05$).

The B or intercept information is shown in table 2. Mean control value on both placebo and barbiturate days was 29 mm Hg. At 90 and 135 minutes the CO_2 response curves displayed a dichotomy, in that mean drug intercepts had a greater differential from the control than placebo intercepts. However, standard deviations were extremely large, and $P > 0.05$.

Discussion

The usual steady-state method of obtaining s is to let the patient breathe CO_2-enriched gas mixtures. Ten to 20 minutes usually are required for ventilation to reach a steady level, and to obtain a valid measure two gas mixtures frequently are required. In patients with airway obstruction and deviations from normal ventilation–perfusion ratios, $P_{ET_{CO_2}}$ may not reflect Pa_{CO_2}, which must be measured. The rebreathing method precludes the necessity for analysis of arterial blood, since CO_2 in the lungs and bag leads to equilibrium with blood perfusing the lungs.[2] Once equilibrium is established the partial pressures of inspired and expired end-tidal and Pa_{CO_2} bear a constant relationship and show a nearly parallel rise. Sampling arterial blood while patients rebreathe CO_2 mixtures has confirmed the equilibrium between lung–bag and blood–

TABLE 1. Morphologic Data: Slopes and Intercepts in Six Normal Volunteers

Subject	Sex	Height (cm)	Weight (kg)	Surface Area (square meters)	Control		45 Min		90 Min		135 Min	
					S	B	S	B	S	B	S	B
1. S. E.	M	171	85	1.95	3.5	43	3.5	40	3.8	45	3.5	40
2. J. L.	M	180	78	1.97	2.9	50	2.2	48	3.4	52	3.1	53
3. T. L.	M	173	70	1.81	3.8	41	3.7	40	3.1	35	3.6	42
4. P. R.	F	160	60	1.65	3.1	52	3.5	57	3.3	51	3.3	56
5. J. B. T.	M	168	64	1.70	4.2	41	4.5	41	3.8	43	3.9	39
6. R. E.	M	173	67	1.80	3.3	48	3.2	53	*Felt asleep*		—	—
Mean ± 1 SD					3.5 ± 0.43	46 ± 4	3.4 ± 0.68	48 ± 6	3.5 ± 0.28	45 ± 6	3.5 ± 0.27	46 ± 7

TABLE 2. Slopes and Intercepts before and after Placebo and Drug (9 Patients)*

Patient	Control		45 Min		90 Min		135 Min	
	s	B	s	B	s	B	s	B
1. Sm. Placebo (P)	0.28	29	0.16	−7	0.18	1	0.27	40
Drug (D)	0.30	30	0.23	37	0.14	1	0.20	32
2. Tyl. P	0.71	33	0.77	35	0.76	35	0.89	37
D	1.03	40	0.67	34	0.89	43	0.74	37
3. Cly. P	0.34	13	0.33	18	0.30	31	0.43	21
D	0.69	25	0.97	40	0.51	23	−0.08	−332
4. Glsn. P	0.39	36	0.05	−248	0.13	−80	0.08	−160
D	0.23	−4	0.35	26	0.37	24	0.32	27
5. Nls. P	0.72	43	0.31	19	0.45	30	0.53	37
D	0.57	37	0.11	−79	0.36	22	0.38	27
6. Wgr. P	0.17	32	0.17	27	0.23	39	0.23	39
D	0.17	29	0.11	−145	—	—	—	—
7. Cwn. P	0.25	4	0.33	21	0.29	1	0.30	19
D	0.33	36	0.29	25	0.14	−27	0.20	3
8. Tms. P	0.27	12	0.18	−18	0.18	−12	0.24	8
D	0.33	21	0.70	54	0.30	28	0.47	44
9. Tuse. P	0.48	58	0.13	1	0.17	21	0.13	1
D	0.53	47	0.04	−171	−0.04	400	0.12	12
Mean (P) ± 1 SD	0.40 ± 0.19	29 ± 15	0.27 ± 0.20	−17 ± 84	0.30 ± 0.19	7 ± 35	0.34 ± 0.23	5 ± 66
Mean (D) ± 1 SD	0.44 ± 0.26	29 ± 6	0.39 ± 0.30	−19 ± 83	0.33 ± 0.26	64 ± 128	0.29 ± 0.23	−19 ± 119

* Placebo and drug were administered in random sequence.

gas tensions, and the similar rates of rise of P_{CO_2}.[10] Changes in P_{ETCO_2} may be used, therefore, as a measure of P_{CO_2} stimulus.

Anesthesiologists have used rebreathing methods to study changes of CO_2 response induced by drugs acting on the respiratory system.[11] A large bag initially containing oxygen usually is used, but this delays equilibrium between bag, lung, and blood; and the P_{ETCO_2} does not reflect changes in Pa_{CO_2} until several minutes have elapsed. But in a small rebreathing bag containing a gas mixture with a P_{CO_2} close to $P\bar{v}_{CO_2}$, equilibrium is rapidly established, and both the P_{ETCO_2} and ventilation increase linearly with time. The steady-state method and the rebreathing method give similar results judged by comparable readings of s.[1]

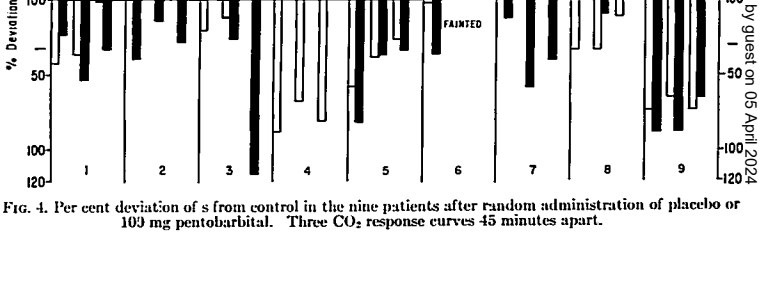

FIG. 4. Per cent deviation of s from control in the nine patients after random administration of placebo or 100 mg pentobarbital. Three CO_2 response curves 45 minutes apart.

TABLE 3. Morphologic Data from Nine Patients

Patient	Sex	Height (cm)	Weight (kg)	Surface Area (sq. meters)
1. Sm. Placebo (P) Drug*† (D)	M	160	45.0	1.42
2. Tyl. P D	F	160	65.4	1.67
3. Cly. P D*‡	M	173	78.2	1.91
4. Glsn. P D*	M	170	60.9	1.69
5. Nls. P D*	M	167	71.3	1.86
6. Wgr. P D*§	M	171	61.2	1.70
7. Cwn. P D	F	155	38.6	1.31
8. Tms. P D	M	160	55.5	1.56
9. Tuse. P D	M	182	45.3	1.57
Mean ± 1 SD		166 ± 8.0	58.0 ± 12	1.63 ± .14

* Fell asleep on this day, but arousable.
† Complained bitterly of sleepiness 48 hours post drug.
‡ Became confused, disoriented during study.
§ Fainted 45 minutes after barbiturate.

Previous studies of normal patients and volunteers indicate that pentobarbital may be a slight respiratory stimulus in the 100-mg dose range and a mild depressant at 200 mg.[12] In spite of this, respiratory failure developed in two of our patients after administration of 100 mg pentobarbital. Our subjects, however, were in chronic respiratory failure and demonstrated respiratory depression prior to the administration of the barbiturate according to the definition of slope[5] (table 2). We administered the drug orally for convenience and acceptability, but measured CO_2 response at the three time intervals mentioned; after two hours and 15 minutes the barbiturate can reasonably be assumed to have been absorbed.[13]

The inability to demonstrate a significant difference between change in slope from control on either barbiturate or placebo day is a key finding of this investigation. It would seem, in fact, that placebo may depress s, since patients 4 and 8 had greater depression on placebo than on barbiturate days, and patients 5 and 9 had almost equal depression on the two days. Although the other five patients showed a clear-cut trend toward greater depression on the barbiturate day than on the placebo day, we conclude that measurements of the ventilation–P_{CO_2} respiratory curve were unable to demonstrate further respiratory depression in this type of severely-ill bronchitic patient given a mild dose of pentobartital. These patients were all in respiratory failure due to severe airway obstruction, and most reached their expected maximum breathing capacities during the procedure.[3] While P_{ETCO_2} was rising, minute volume was not. This is in contrast to the linear increase in both parameters in normal patients during the CO_2 response test (figs. 2 and 3). Administration

TABLE 4. Mixed Venous $P\bar{v}_{CO_2}$ and FEV_1/VC before and after Placebo and Drug

Patient	Control		45 Min		90 Min		135 Min	
	$P\bar{v}_{CO_2}$	FEV_1/VC	$P\bar{v}_{CO_2}$	FEV_1/VC	$P\bar{v}_{CO_2}$	FEV_1/VC	$P\bar{v}_{CO_2}$	FEV_1/VC
1. Sm	73 71	0.5/1.7 0.4/1.6	73 73	0.5/1.5 0.4/1.6	75 73	0.6/1.7 0.4/.75	74 70	0.5/1.5 0.4/.75
2. Tyl	54 53	1.0/1.6 0.9/1.6	53 53	1.0/1.6 0.9/1.5	55 56	1.2/1.9 0.9/1.7	54 55	1.0/1.8 1.0/1.8
3. Cly.	58 59	0.9/2.6 0.8/2.3	59 58	0.9/2.8 0.6/1.2	58 57	0.9/2.9 0.2/0.9	58 57	0.9/2.6 0.7/1.1
4. Glsn.	59 61	0.6/1.9 0.6/2.3	58 60	0.7/2.0 0.7/2.3	60 65	0.6/1.9 0.7/2.9	61 63	0.6/1.8 0.7/2.1
5. Nls.	58 56	0.8/1.6 0.8/1.6	55 57	0.8/1.7 0.8/1.8	56 57	0.8/1.7 0.8/1.7	59 58	0.9/1.7 0.8/1.7
6. Wgr.	77 84	0.5/1.8 —	78 83	0.4/1.9 *Syncope*	75 —	0.4/2.1 —	78 —	0.4/2.0 —
7. Cwn.	62 58	0.9/2.2 0.8/2.2	62 59	0.9/2.2 0.8/2.1	61 58	0.9/2.1 0.9/2.1	57 59	1.0/2.1 1.0/2.1
8. Tms.	65 62	0.5/1.1 0.5/0.9	64 64	0.5/0.9 0.5/0.9	61 63	0.5/0.8 0.5/0.9	59 64	0.5/1.0 0.4/1.0
9. Tusc.	71 72	0.7/2.2 0.8/2.4	71 74	0.7/2.4 0.8/2.3	74 74	0.7/2.2 0.8/2.4	71 70	0.7/2.1 0.7/2.1
Mean ± 1 SD, P	64 ± 7.5	0.7 ± .18/1.9 ± 0.4	64 ± 8.1	0.7 ± 0.19 1.9 ± 0.52	64 ± 7.9	0.7 ± 0.23 1.9 ± 0.52	63 ± 8.1	0.7 ± 0.22 1.8 ± 0.42
Mean ± 1 SD, D	64 ± 9.3	0.7 ± .15/1.9 ± 0.5	65 ± 9.3	0.7 ± 0.16 1.7 ± 0.48	63 ± 6.8	0.6 ± 0.24 1.7 ± 0.73	62 ± 5.4	0.7 ± 0.21 1.6 ± 0.52

of a drug would make little difference in this instance in such a bronchitic patient pushed to the limits of breathing performance. It is also conceivable that in certain patients 100 mg pentobarbital per 70 kg of body weight may stimulate ventilatory response to CO_2.[12,14]

It has been demonstrated that a poor correlation exists between FEV_1 and s,[10] a finding confirmed by this study. In fact, spirometry changed little during a given test day or in the same patient from day to day. Although the barbiturate had a definite sedative effect which was more marked than expected, no change in $P\bar{v}_{CO_2}$ was noted during the study; a delayed increase occurred in two patients. With the exception of patient 6, $P\bar{v}_{CO_2}$ in each patient was similar from day to day. Patient 6 fainted after recording of the second curve on the drug day, but the study was included since a complete set of placebo curves had already been obtained. The high control value for mean and individual $P\bar{v}_{CO_2}$ values reflects the severity of illness and the relative similarity among the nine patients with respect to CO_2 retention.

The degree of central nervous system depression in five patients was a matter for concern: patients in respiratory failure appeared to be unduly sensitive to the sedative effects of barbiturates. In spite of this, depression of alveolar ventilation, as assessed by a rise in $P\bar{v}_{CO_2}$, occurred in two patients only and was delayed several hours. These two patients developed $P\bar{v}_{CO_2}$ values approximately 10 mm Hg higher than the controls after the study was concluded, and they had to be treated with controlled oxygen therapy.[15] In the group as a whole, however, there was no significant depression. There is, therefore, a dichotomy between the development of further CO_2 unresponsiveness ("respiratory depression") and central nervous system depression in these patients under the conditions described. The barbiturate clearly demonstrated cortical depression and, eventually, in two patients, caused enough obtundation of the central nervous system to create harm. This was not assessed with prediction by the CO_2 response curve for the group examined as a whole. However, in patients 3 and 6, the respiratory failures-to-be, the s depression was significantly greater with barbiturates. Patient 6, in fact, fainted at the end of the recording of the 45-minute curve and we deemed it unwise for him to proceed further. On the other hand, the measuring technique may be relatively insensitive. Thus, any change in s measured

may be difficult to demonstrate in these patients, since it has a small absolute value. A decrease in s of 0.5 l/min/mm Hg from a level of 3.0 in all patients or volunteers represents a fall of approximately 17 per cent and is clearly measurable, but a decrease in s of 0.1 l/min/mm Hg from a level of 0.6 in a bronchitic patient (as in our study), while a similar percentage drop, is a barely measurable absolute decrease.

The greater deviation from the control in B or intercept on the day when the barbiturate was administered when compared with the placebo is difficult to interpret. There is poor definition of intercept in biologic terms, and Lambertsen and Kellogg question its use, meaning and significance.[16,17]

Conclusions

We studied nine bronchitic patients with known severe airway obstruction, average $P\bar{v}_{CO_2}$ of 64 mm Hg, and average FEV_1/VC of 0.7/1.9 l. Their ventilatory responses to CO_2 were investigated on two separate days by administering either a placebo ($s = 0.40 \pm 0.19$ l/min/mm Hg) or 100 mg pentobarbital ($s = 0.44 \pm 0.26$ l/min/mm Hg) orally, in double-blind fashion. The barbiturate did not alter the slope of the ventilation P_{CO_2} response curve significantly in these patients. In addition, changes in $P\bar{v}_{CO_2}$ and FEV_1/VC were minimal and similar on both days. Five patients exhibited signs of central nervous system depression with the administration of barbiturate but not with the placebo; this depression was out of proportion to the dose; three developed potentially serious complications and two entered respiratory failure. Three developed potentially serious sedation and in two, respiratory failure was increased. We concluded that patients in respiratory failure are very sensitive to the sedative effects of barbiturate. If sedation is needed, small doses should be used and P_{CO_2} should be monitored.

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