

Effects of Propiomazine on Respiration and Circulation

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The effect of 30 mg./70 kg. of propiomazine on the respiratory response to endogenously accumulated CO₂ was measured in 5 volunteers and found to have no depressant action. Irregular, sighing respiration was noted, however. Three of 9 volunteers given 30 mg./70 kg. propiomazine became quite hypotensive when suddenly tilted head-up 60 degrees. Approximately one half the subjects became restless after injection of propiomazine. It was concluded that the optimal use of the drug is in conjunction with small doses of narcotics. Propiomazine is pharmacologically very similar to its related compound promethazine in its lack of respiratory depression but positive circulatory depressing action.

A NEW tranquilizer has become available for clinical use, the structure and action of which is similar to promethazine; however, it is purported to be more potent, with a more rapid onset and a shorter duration of action.

Eckenhoff¹ and Miller² have reported data on the effects of promethazine on circulation and respiration. We have undertaken a similar investigation of propiomazine to study its effects primarily upon respiration and circulation, to find out if the slight alteration in molecular structure of promethazine alters the pharmacological effects.

Methods

Respiratory studies were carried out on 5 volunteers ranging from 20 to 40 years of age. The carbon dioxide response test was used with a technique similar to that used by Eckenhoff.³ The subject breathed through a closed circuit containing a soda lime cannister which

could be excluded with ease. An infrared CO₂ analyzer with a breathe-through cell was inserted on the expiratory side of a unidirectional valve at the face of the subject. A 9 liter Collins spirometer was included in the circuit. For control studies, resting minute volume was recorded allowing several minutes to obtain a steady state. The CO₂ absorber was then switched out of circuit and carbon dioxide allowed to accumulate. End-expiratory CO₂ was monitored continuously to correlate with minute volume. The response to endogenously accumulated CO₂ was carried out for approximately ten minutes. The subject was then disconnected from the circuit and allowed to rest for ten to fifteen minutes. Propiomazine in a dose of 30 mg./70 kg. was given intravenously and ten minutes later, the respiratory response to endogenously accumulated CO₂ was measured again.

For circulatory studies, a tilt test was used on 9 healthy volunteers ranging in age from 20 to 40 years. Subjects were tilted head-up 60 degrees rapidly on a standard operating table and maintained in that position for 15 minutes. The table was then levelled and the subjects were given propiomazine 30 mg./70 kg. intravenously and 5-10 minutes later again tilted. Blood pressures were recorded intermittently by auscultation with a stethoscope and cuff strapped on the subject's arm maintained at the level of the aortic arch.

Results

Table 1 presents the respiratory data obtained from 5 volunteers. The five subjects showed an increase in minute volume of 2.5 to 5.5 times over the resting state in response to rebreathing CO₂. Following the injection of propiomazine, two subjects D. B. and A. B. seemingly had respiratory depression. However, it was the impression of the observer that their resting minute volumes prior to propio-

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TABLE 1. Respiratory Response to Carbon Dioxide Before and After the Intravenous Administration of 30 mg./70 kg. of Propiomazine

		Before Propiomazine				After Propiomazine			
		Resting	CO ₂ Elevated	Change	Percentage Increase	Resting	CO ₂ Elevated	Change	Percentage Increase
P. B.	PE CO ₂	33	48			33	38		
	RR	10	18			14	19		
	MV	5.5	22.5	17	409	5.0	26.3	21.3	526
R. J.	PE CO ₂	37	48			35	50		
	RR	12	18			18	24		
	MV	5.6	30	24.4	534	12.5	33.7	21.2	269
D. B.	PE CO ₂	40	56			43	58		
	RR	15	17			15	18		
	MV	8.8	20	11.2	227	5.0	17.5	12.5	350
A. B.	PE CO ₂	36	50			41	49		
	RR	14	16			12	20		
	MV	10	30	20	300	4.5	30	25.5	667
W. G.	PE CO ₂	48	67			41	67		
	RR	12	16			16	17		
	MV	10	45	35	450	8.0	47.5	39.5	594
Mean	PE CO ₂	38	54			39	54		
	RR	12	17			15	20		
	MV	8	29	21	350	7	31	24	443

PE CO₂ = end expiratory Pco₂; RR = respiratory rate; MV = minute volume in liters/minute.

mazine were abnormally elevated owing to apprehension. In each instance, the response to rebreathing CO₂ after propiomazine was practically the same as or greater than that prior to the drug for similar levels of end-expiratory Pco₂. Thus it appears that propiomazine did not depress the response to elevated CO₂. The same respiratory pattern was noted as reported by Eckenhoff¹ for promethazine, namely, an irregular, sighing type of respiration interspersed by shallow, jerky breaths.

The responses of blood pressure and pulse rate of 60 degree head-up tilting are presented in table 2. Although all the subjects demonstrated a mean decrease in systolic blood pressure of 17 per cent, none showed symptoms of fainting during the control study. Five showed some degree of tachycardia after tilting with an increase in mean pulse rate of 16 beats per minute. Following the administration of propiomazine and tilting, all the subjects exhibited a rise in pulse rate from 13 to

106 per cent above the pre-tilt value with a mean increase of 44 per cent. Three of the 9 subjects became hypotensive with impending faint and were returned to the level position with immediate relief of symptoms. Two other subjects, J. B. and R. T. found it impossible to cooperate with the test and moved about, flexing their extremities while tilted. Had they been able to lie perfectly still they may well have fainted. By palpation of the radial artery, it appeared that there were wide variations in blood pressure, however, this could not be readily detected because of difficulty with the auscultatory method for measuring blood pressure.

Following the intravenous administration of propiomazine to subjects undergoing respiratory and circulatory studies, phenomena similar to those reported by both Eckenhoff and Millar for promethazine were observed. Within 30-60 seconds, subjects reported a sensation of warmth, lethargy, drowsiness, heaviness, and inability to move. Within approximately

TABLE 2. Response to Sudden 60 Degree Head-Up Tilting 10 Minutes Following the Intravenous Administration of 30 mg./70 kg. Propiomazine

	Before Tilt		Control Tilt				Tilt after Propiomazine				Comment
	B.P.	P.	Low B.P.	% Change Systolic	High P.	% Change	Low Blood Pressure	% Change Systolic	High P.	% Change	
D. M.	130/80	108	110/75	-15	90	-17	70/50	-46	132	+22	nausea, faint 15 min. pulse 66
T. R.	140/90	76	125/95	-11	108	+42	70/40	-50	102	+34	faint 7 min. pulse 50
P. B.	110/60	72	105/60	-4.5	96	+33	60/40	-15	84	+17	pale, faint 5 min.
J. B.	118/70	80	90/50	-24	80	0	80/65	-32	132	+65	restless
R. T.	120/80	66	108/75	-10	78	+18	110/80	-8	120	+82	restless
D. B.	160/95	108	150/90	-6	108	0	120/100	-25	120	+13	
M. R.	130/80	72	120/75	-8	90	+25	120/80	-0	90	+25	
R. J.	130/78	70	115/80	-11	96	+37	115/90	-11	144	+106	
J. R.	112/80	90	108/70	-11	96	+7	105/70	-14	120	+33	
Mean				-17		+16		-26		+44	

B. P. = auscultatory blood pressure; P. = pulse rate.

ten minutes several subjects became quite restless, despite drowsiness and moved about continuously. Sensations such as "wanting to jump out of my skin," and "impending doom" were reported.

Three of 5 subjects who had respiratory studies and 6 of 9 subjects who were tilted experienced the phenomenon of restlessness despite drowsiness. The subjects found it practically impossible to lie still and thrashed about continually. The restlessness and agitation was of from one to four hours duration. Drowsiness persisted up to eight hours. Another phenomenon experienced by practically all subjects was marked dryness of the mouth.

We have used propiomazine in conjunction with narcotics for sedation on many occasions. Doses of 20 mg. of propiomazine in conjunction with 50 mg. of meperidine have produced excellent sedation in that patients tolerated discomfort and were also sleepy. This combination has been used for patients who became restless during spinal anesthesia. It has also been useful for postoperative restlessness. Meperidine seems to obtund the restlessness which frequently results from propiomazine, and propiomazine produces more drowsiness than meperidine alone. However, hypotension has been noted in elderly patients with combinations of this drug.

Discussion

From the data obtained, it appears that propiomazine has properties similar to promethazine with respect to respiration and circulation in that the response to elevated CO_2 was not altered significantly but the pattern of normal respiration is. Propiomazine is a depressor of circulatory readjustments to the head-up position in doses which produce sedation. This probably represents interference with reflex vasoconstriction.

Grimaldi⁴ reported on the usefulness of propiomazine for sedation during labor when given intravenously but also noted the circulatory depressant effects. Davis and Jenicek⁵ reported on the usefulness of propiomazine when used in conjunction with meperidine. Lear⁶ reported that propiomazine was a satisfactory adjunct to spinal anesthesia. However, his patients had already received a barbiturate and meperidine preoperatively, which probably masked the undesirable effects of propiomazine.

The CO_2 response test was attempted in 13 patients scheduled for elective surgery. The studies could not be completed however because of uncooperativeness especially after propiomazine administration. It is our impression that the patients did not have sufficient motivation to complete the test since breathing 6 per cent carbon dioxide is quite uncomfortable. Emotional liability to the point

of uncontrollable sobbing was noted in one patient.

It is paradoxical that the phenothiazines, frequently classified as tranquilizers, actually produce the opposite effect. One must keep in mind, however, that volunteers may behave differently from preoperative patients. Because of the unpredictability of response we suggest that these agents should not be used alone for sedation, as recommended by the manufacturer.

Summary

Propiomazine, a new phenothiazine compound similar to promethazine, was subjected to a clinical and laboratory evaluation. In sedative doses of 30 mg./70 kg., given intravenously the response to accumulated CO₂ was not depressed and an irregular respiratory pattern similar to that produced by promethazine was seen. Three of 9 subjects given the same dose of propiomazine had severe hypotension when tested for circulatory responses to tilting, indicating a depressor action of the drug.

When given intravenously as the sole agent, the drug produced a 60 per cent incidence of restlessness, confusion and agitation in volunteers. The optimal use for the drug appeared to be in combination with a narcotic, as recommended by the manufacturer.

References

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TRACHEAL MOTION Changes in circumferential and longitudinal dimensions of the tracheobronchial tree were studied in dogs during both spontaneous and artificial ventilation using mercury strain gauges which had been sutured to the airway wall. Changes in airway circumference related to changes in airway transmural pressure and changes in airway length related to overall descent of the lungs occurring with each respiratory cycle. In addition, tonic tracheoconstriction and slow rhythmic changes in airway caliber occurred. Both were mediated by the vagus nerve. Changes in airway volume were calculated from length-circumference data. No evidence of tracheal peristalsis was observed. (Scarpelli, E. M., Rea, F. J. P., and Rudolph, A. M.: *Tracheal Motion During Eupnea*, *J. Appl. Physiol.* 20: 473 (May) 1965.)

OXYGEN TOXICITY PROTECTION Anesthesia is known to protect against convulsions caused by oxygen at high pressure. The present study demonstrated that sodium pentobarbital anesthesia protected rats against both convulsions and pulmonary damage caused by exposure to oxygen at 70-75 PSI. Protection was equally effective in both control animals and in those whose metabolism was artificially increased by administration of dinitrophenol or L-thyronine or electrical stimulation of muscle. The observed protection was therefore not due simply to depression of metabolism by anesthesia. Pulmonary damage and convulsions due to hyperbaric oxygen are not separate entities. Central and neurogenic factors may be of importance in causation of pulmonary damage under these circumstances. (Bean, J. W., and Zee, D.: *Metabolism and the Protection by Anesthesia Against Toxicity of O₂ at High Pressure*, *J. Appl. Physiol.* 20: 525 (May) 1965.)