INFLUENCE OF OPIATES ON THE RESPIRATORY RESPONSE OF MAN TO THIOPENTAL

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CONSIDERABLE attention has been directed toward the respiratory and circulatory depressant properties of thiopental. Many of the observations have been made on animals, subjects, or patients given an opiate prior to the administration of thiopental (1–6). Data to be presented in this paper indicate that the preanesthetic administration of opiates interferes with a valid appraisal of the respiratory effects of thiopental. A quantitative study of this problem has been attempted.

METHODS

The subjects in this study were normal, healthy volunteers between the ages of 20 and 30 years, or essentially healthy patients scheduled for minor operative procedures. Four of the subjects participated in paired studies, that is, they first received an opiate before being given thiopental, and approximately a week later received thiopental alone. Studies were completed on the patients prior to the operation. The technique employed in making and recording the respiratory measurements has been described in detail elsewhere (7). The apparatus consisted of a closed circle system incorporating a 6-liter recording spirometer, an infrared carbon dioxide analyzer (Liston-Becker), an oscillograph, carbon dioxide absorption canisters which could be shunted out of the system, and a set of valves (Stephen-Slater) to provide unidirectional flow of gases.

Control observations were made of respiratory rate, tidal volume, and end-expiratory carbon dioxide concentration. Minute volume of respiration and pCO_2 were calculated. The respiratory response to endogenously accumulated carbon dioxide (canister shunted out of system) was then measured (8, 9, 10). Similar measurements were made after the administration of the drugs being studied. In many instances duplicate runs were made to demonstrate the reproducibility of control, opiate, or thiopental effect.

Thiopental was administered intravenously as a 0.2 per cent drip. The total dose was approximately 500 mg. in twenty to twenty-five

Read before the annual meeting of the American Society of Anesthesiologists in Boston, Mass., November 1, 1955, and accepted for publication January 5, 1956. The authors are in the Department of Anesthesiology, Hospital of the University of Pennsylvania, and the Harrison Department of Surgical Research, University of Pennsylvania School of Medicine in Philadelphia. The work was supported by a research grant (DA-29-007-MD-599) from the Department of the Army.

minutes. At the time observations were made, these individuals were unconscious, tolerated the rubber mouthpiece, usually required support of the mandible, and did not respond to superficial painful stimuli. Most of them, however, were judged not to be sufficiently anesthetized for surgical intervention. Those whose electroencephalograms were available were between levels 1 and 2 as described by Kiersey *et al.* (11). Brachial arterial or antecubital venous samples were drawn at

TABLE 1

RESPIRATORY EFFECTS OF THIOPENTAL

		Control		Thiopental	
		Control	CO_2	Control	CO_2
W. B., white, male 63 yrs., Ht. 67" Wt. *132 lbs.* No preanesthetic medication --- Thiopental 21 mg./L	End exp. pCO_2 (mm. Hg) Resp. rate/min. Tidal vol. (cc.) Min. vol. (L/min.)	44 13 245 3.2	69 14 610 8.5	44 15 240 3.6	70 20 910 18.2
A. M., white, male 36 yrs., Ht. 71" Wt. *158 lbs.* No preanesthetic medication --- Thiopental 13.7 mg./L	End exp. pCO_2 Resp. rate/min. Tidal vol. (cc.) Min. vol. (L/min.)	38 18 310 5.6	53 25 750 18.8	38 16 350 5.6	54 23 1110 25.5
M. N., white, male 30 yrs., Ht. 66" Wt. *140 lbs.* No preanesthetic medication --- Thiopental 12.8 mg./L	End exp. pCO_2 Resp. rate/min. Tidal vol. (cc.) Min. vol. (L/min.)	40 18 260 4.7	61 26 1030 26.8	41 15 290 4.4	62 22 1440 31.7
S. C., colored, female 35 yrs., Ht. 68" Wt. *135 lbs.* Atropine 0.4 mg. --- Thiopental 19.9 mg./L	End exp. pCO_2 Resp. rate/min. Tidal vol. (cc.) Min. vol. (L/min.)	40 16 310 5.0	60 23 840 19.3	40 14 360 5.0	59 22 840 18.5
S. C., colored, female 35 yrs., Ht. 68" Wt. *135 lbs.* Atropine 0.4 mg. --- Thiopental 14.9 mg./L	End exp. pCO_2 Resp. rate/min. Tidal vol. (cc.) Min. vol. (L/min.)	40 16 310 5.0	60 23 840 19.3	40 18 310 5.6	59 19 740 14.1
F. K., white, female 33 yrs., Ht. 63" Wt. *113 lbs.* Atropine 0.4 mg. --- No level	End exp. pCO_2 Resp. rate/min. Tidal vol. (cc.) Min. vol. (L/min.)	45 19 230 4.4	60 16 490 7.8	43 20 240 4.8	60 21 350 7.4

TABLE 1—*Continued*

		Control		Thiopental	
		Control	CO_2	Control	CO_2
V. W., colored, female	End exp. pCO_2	40	53	39	53
43 yrs., Ht. 66"	Resp. rate/min.	14	16	14	16
Wt. *150 lbs.*	Tidal vol. (cc.)	200	570	335	740
No preanesthetic medication	Min. vol. (L/min.)	2.8	9.1	4.7	11.8
No level					
V. W., colored, female	End exp. pCO_2	40	53	40	52
43 yrs., Ht. 66"	Resp. rate/min.	14	16	15	13
Wt. *150 lbs.*	Tidal vol. (cc.)	200	570	320	600
No preanesthetic medication	Min. vol. (L/min.)	2.8	9.1	4.8	7.8
No level					
E. W., colored, female	End exp. pCO_2	44	60	44	62
55 yrs., Ht. 64"	Resp. rate/min.	12	16	12	18
Wt. *125 lbs.*	Tidal vol. (cc.)	340	860	400	670
No preanesthetic medication	Min. vol. (L/min.)	4.1	13.8	4.8	12.5
No level					
A. B., white, male	End exp. pCO_2	47	63	45	63
24 yrs., Ht. 68"	Resp. rate/min.	6	14	12	16
Wt. *155 lbs.*	Tidal vol. (cc.)	560	1280	278	1220
No preanesthetic medication	Min. vol. (L/min.)	3.36	17.92	3.34	19.52
Thiopental 11.8 mg./L					
M. F., white, female	End exp. pCO_2	33	58	39	58
29 yrs., Ht. 65"	Resp. rate/min.	13	18	9	18
Wt. *108 lbs.*	Tidal vol. (cc.)	260	1460	340	1430
No preanesthetic medication	Min. vol. (L/min.)	3.4	26.3	3.0	25.5
Thiopental 9.9 mg./L					
W. G., white, male	End exp. pCO_2	40	53	40	53
25 yrs., Ht. 70"	Resp. rate/min.	9	20	14	16
Wt. *160 lbs.*	Tidal vol. (cc.)	340	1280	340	720
No preanesthetic medication	Min. vol. (L/min.)	3.1	25.0	4.8	11.5
Thiopental 9.3 mg./L					

appropriate intervals and analyzed for thiopental by the method of Brodie *et al.* (12). The opiates, morphine sulfate (10–15 mg.) or meperidine hydrochloride (75–100 mg.), were administered intramuscularly in combination with atropine sulfate (0.4 mg.). A minimum of forty-five minutes was allowed to elapse following injection

of the opiate before the respiratory functions and response to carbon dioxide were first measured.

RESULTS

Thiopental.—The effects of thiopental upon respiration were measured in 12 individuals who received no preanesthetic medication or who received atropine sulfate only. These results are presented in table 1 and summarized in table 2. In 9 subjects there was no change from the control end-expiratory pCO_2 during thiopental anesthesia, whereas 2 showed a decrease and 1 an increase. The respiratory rate was unaltered in 6 subjects, increased in 3 and decreased in 3. The effect on minute volume was also variable: there was no change in 4 subjects, an increase in 6, and a decrease in 2. The respiratory minute volume response to endogenously accumulated carbon dioxide was increased from 9 per cent to 114 per cent in 5 of the subjects and decreased from 4 per

TABLE 2

EFFECT OF THIOPENTAL ON RESPIRATION
(Change Expressed as % of Control Values)

Subject	pCO_2	Rate	Minute Volume	Response to CO_2
W. B.	0	0	0	+114
A. M.	0	0	0	+36
M. N.	0	−19	−6	+19
S. C.	0	−12	0	−4
S. C.	0	+12	+12	−27
F. K.	−4	0	+9	−5
V. W.	0	0	+68	+30
V. W.	0	0	+71	−16
E. W.	0	0	+17	−10
A. B.	−4	+100	0	+9
M. F.	+18	−30	−12	−5
W. G.	0	+55	+54	−54

cent to 54 per cent in the remaining 7. The average alteration in response to increased carbon dioxide was an increase of 7 per cent over the control value.

Thiopental Following Opiate.—The respiratory effects of thiopental following the intramuscular injection of morphine sulfate or meperidine hydrochloride in 6 subjects are presented in table 3 and summarized in table 4. The response of one individual who received secobarbital sodium (100 mg.) intramuscularly prior to thiopental administration is included for comparison. In those subjects receiving opiates and thiopental, end-expiratory pCO_2 increased in 3 cases and remained unchanged in 3. Respiratory rate was elevated in 3 individuals and lowered in 3. Minute volume was unaltered in 2 subjects, reduced in 3, and raised in the other. The response to carbon dioxide was diminished in all 6 individuals. The average reduction was 54 per cent, with a range of 40 to 74 per cent.

TABLE 3—EFFECT OF OPIATE AND THIOPENTAL ON RESPIRATION

		Control		Thiopental	
		Control	CO_2	Control	CO_2
B. W., white, male 19 yrs., Ht. 69″ Wt. *138 lbs.* Meperidine 100 mg. Atropine 0.4 mg. --- Thiopental 7.8 mg./L	End exp. pCO_2 (mm. Hg)	48	70	49	69
	Resp. rate/min.	15	20	13	18
	Tidal vol. (cc.)	290	990	250	680
	Min. vol. (L/min.)	4.4	19.8	3.3	12.2
B. W., white, male 19 yrs., Ht. 69″ Wt. *138 lbs.* Meperidine 100 mg. Atropine 0.4 mg. --- Thiopental 18.9 mg./L	End exp. pCO_2	48	70	53	69
	Resp. rate/min.	15	20	17	19
	Tidal vol. (cc.)	290	990	230	270
	Min. vol. (L/min.)	4.4	19.8	3.9	5.1
M. F., white, female 29 yrs., Ht. 65″ Wt. *108 lbs.* Meperidine 75 mg. Atropine 0.4 mg. --- Thiopental 8.2 mg./L	End exp. pCO_2	36	55	43	54
	Resp. rate/min.	16	18	14	16
	Tidal vol. (cc.)	270	1130	310	690
	Min. vol. (L/min.)	4.32	20.34	4.36	11.06
A. B., white, male 24 yrs., Ht. 68″ Wt. *155 lbs.* Meperidine 100 mg. Atropine 0.4 mg. --- Thiopental 8.6 mg./L	End exp. pCO_2	47	61	47	61
	Resp. rate/min.	7	14	11	14
	Tidal vol. (cc.)	340	1160	280	690
	Min. vol. (L/min.)	2.4	16.2	3.1	9.7
R. J., white, male 31 yrs., Ht. 67″ Wt. *150 lbs.* Morphine sulfate (12 mg.) Atropine 0.4 mg. --- Thiopental 9.4 mg./L	End exp. pCO_2	43	60	44	60
	Resp. rate/min.	9	12	10	11
	Tidal vol. (cc.)	360	1320	320	740
	Min. vol. (L/min.)	3.24	15.84	3.2	8.14
W. G., white, male 25 yrs., Ht. 70″ Wt. *160 lbs.* Morphine sulfate (12 mg.) Atropine 0.4 mg. --- Thiopental 11.6 mg./L	End exp. pCO_2	41	59	46	59
	Resp. rate/min.	12	18	11	12
	Tidal vol. (cc.)	380	1420	260	540
	Min. vol. (L/min.)	4.6	25.6	2.8	6.5
O. W., colored, female 30 yrs., Ht. 68″ Wt. *147 lbs.* Secobarbital 100 mg. Atropine 0.4 mg. --- Thiopental 19.0 mg./L	End exp. pCO_2	34	53	34	54
	Resp. rate/min.	20	22	17	24
	Tidal vol. (cc.)	230	670	270	605
	Min. vol. (L/min.)	4.6	14.7	4.6	14.5

TABLE 4

EFFECT OF OPIATE AND THIOPENTAL ON RESPIRATION
(Change Expressed as % of Control Values)

Subject	pCO_2	Rate	Minute Volume	Response to CO_2
B. W. (D)	0	−13	−25	−42
B. W. (D)	+10	+13	−11	−74
M. F. (D)	+19	−12	0	−46
A. B. (D)	0	+57	+ 2	−40
R. J. (M)	0	+11	0	−49
W. G. (M)	+12	− 8	−39	−74
O. W. (S)	0	−15	0	− 1

D—Meperidine. M—Morphine. S—Secobarbital.

Data in the case in which secobarbital was administered showed no significant alteration following thiopental other than a 15 per cent decrease in respiratory rate, which was offset by a similar increase in tidal volume.

DISCUSSION

These data indicate that respiratory depression produced by thiopental alone, in the dosage range studied, was minimal. In some individuals there was even improvement in respiratory response to carbon dioxide following thiopental. It was thought at first that this observation might be attributed in part to the fact that the patients were apprehensive and the control data did not represent a normal response to carbon dioxide. The study was therefore completed on volunteer subjects. These relaxed individuals, who were neither anxious nor tense, reacted in similar fashion, so that other explanations must be sought.

In marked contrast to this was the profound * respiratory depression recorded in the individuals receiving thiopental after injection of morphine or meperidine. The question which naturally arises is: Was the respiratory depression noted in the second group of individuals due only to the opiates, or were the opiate and thiopental synergistic rather than additive? In a study of the effect on respiration of a large variety of opiate and opiate-like drugs, the average depression in response to endogenously accumulated carbon dioxide was of the same order of magnitude as that exhibited by the individuals who received thiopental following an opiate (13). On the basis of these findings, it is our present opinion that the major part of the respiratory effect of the combination was due to the opiate, and that the addition of the thiopental caused little further respiratory depression.

Opiates almost invariably produce a rise in resting end-expiratory

* Statistical analysis of the difference between opiate-thiopental and opiate alone by the Fischer T method: $p < .01$.

pCO_2 ranging from 2 to 12 mm. of mercury, and a sharply diminished respiratory response to endogenously accumulated carbon dioxide as measured by minute volume. The effects upon respiration may progress or persist at their maximum for as long as five hours. The use of "control" measurements taken before or shortly after opiate administration may vary considerably from "control" readings an hour or two later when opiate depression may have progressed. In addition to the above, one must also take into account that the respiratory effects of two depressants acting simultaneously may be entirely different from that of the two depressants acting individually.

These data support the belief that measurements of respiratory rate and minute volume alone may be misleading in determining the degree of respiratory depression. M. F. (table 4) showed no change in respiratory minute volume and only a 12 per cent decrease in rate, yet her resting end-expiratory pCO_2 had risen 19 per cent, and her response to carbon dioxide revealed a 46 per cent depression. Similarly A. B. (table 4) showed an increase in both rate and minute volume yet his response to carbon dioxide had diminished 40 per cent.

The effect of thiopental following secobarbital is in keeping with earlier observations (9) that barbiturates in the doses commonly employed for pre-anesthetic medication have an insignificant effect upon respiration.

It would appear, therefore, that if the respiratory depressant effects of the opiates are so marked and those of thiopental as studied here are minimal, it is unprofitable to attempt to study the relatively small changes due to thiopental in the presence of the large changes introduced by opiates.

The problem of defining the degree of depression, or as it is termed clinically "the depth of anesthesia" during thiopental administration is far from solved. Consider the objective methods available: First, the blood levels of thiopental. These are subject to wide individual variation even when the rate of injection, total dose, and concentration are rigidly controlled. When the initial dose is variable, the phenomenon of "acute tolerance" may be introduced and further decrease the reliability of blood levels in reflecting depth of anesthesia (14, 15). Secondly, total dose per unit time has been used, but here again the influence of the size and rate of the initial injection may make this method totally unreliable. Third, electroencephalographic levels have been defined and correlated with the clinical depth of anesthesia. These are, however, not well correlated with blood levels of thiopental. Lastly, depression of reflex response to electrical stimulation has been used as a method of determining the depth of anesthesia (16, 17).

Clinical signs of depth of thiopental anesthesia are also of questionable reliability when attempts are made to correlate them with objective measurements. The classical signs, so useful for diethyl ether, are of much less use during thiopental anesthesia. Movement, phona-

tion, and laryngospasm in response to surgical manipulation are not only inconstant guides of depth of anesthesia, but are also undesirable for obvious reasons. We must admit, therefore, that the determination of depth of thiopental anesthesia is difficult to define qualitatively.

Our data concerning the lack of respiratory depression from thiopental should not be misconstrued. Thiopental administered in sufficient dosage does result in respiratory depression even in normal individuals. It is evident that all of the individuals included in this study were relatively lightly anesthetized, as judged by their clinical signs, blood levels, electroencephalographic levels, rate of administration, and total dosage.

SUMMARY

Data on normal volunteers or relatively healthy patients have been presented to show that the respiratory depressant effect of thiopental over a relatively wide blood level range is minimal. Following preanesthetic medication with opiates, respiratory depression with thiopental is profound.

The errors inherent in studying the respiratory depressant effects of a slightly depressant drug (thiopental) in the presence of a markedly depressant one (opiate) are discussed.

The problem of determining depth of thiopental anesthesia is considered.

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