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SHIVERING FOLLOWING THIOPENTAL SODIUM AND OTHER ANESTHETIC AGENTS * † ‡

ROBERT M. SMITH, M.D., § LEONARD BACHMAN, M.D., ||
AND THINA BOUGAS, M.D. ¶
Boston, Massachusetts

MANY anesthesiologists have from time to time observed patients who showed marked, generalized tremor following anesthesia with thiopental sodium. This phenomenon is known to some by the informal term "Pentothal shakes" (1). Although several varied theories as to the cause of the tremor have been voiced, no careful study has been undertaken to determine its origin or significance. Of the theories entertained, several point to errors in technique, such as pyrogen reaction, carbon dioxide excess, or hypoxia (2); others blame specific effects of the drug, such as its reputed "depression of the temperature regulating center."

Our interest in the subject was aroused by observation of a high incidence of shaking following thiopental, and the occasional occurrence of similar tremor following ether anesthesia. Since faulty technique had been named as the possible cause of such reactions, further investigation seemed indicated. At the outset two obvious factors seemed of possible significance: [1] our operating rooms were often cold, and [2] our patients were children.

METHOD

Observations were made on 259 patients, all basically healthy and without metabolic or neurologic disorders. Ages ranged from 6

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§ Director of Anesthesia.

|| Former Resident in Anesthesia.

¶ Associate Anesthesiologist.

months to 18 years, and patients were of both sexes. Anesthetic agents included intravenous thiopental sodium with semiclosed nitrous oxide-oxygen supplementation; ether by open, insufflation, and closed techniques; and cyclopropane by closed techniques. Nitrous oxide-oxygen was given in flows varying from 6 liters nitrous oxide; 2 liters oxygen to 1 liter nitrous oxide; 1 liter oxygen. Respiration was assisted in all cases where semiclosed or closed techniques were used. Thiopental was administered in 2.5 per cent solution by intermittent injection into a 5 per cent dextrose and water intravenous drip, or by direct intravenous injection.

Special precautions were taken to exclude pyrogen reactions. Freshly prepared thiopental was used, mixed with pyrogen-free distilled water. In the first 75 cases rubber-tubed intravenous sets were used such as are standard in our hospital. The above sets cause less than 1 per cent pyrogen reactions when used on conscious ward patients and were thought to be satisfactory. As a further precaution, however, in the remaining 45 patients receiving thiopental only newly prepared rubber-tubed sets, or plastic disposable sets, were used. The incidence of tremor proved strikingly similar with all type of apparatus. That the tremors in this study were not due to pyrogen chills was attested by the absence of temperature elevation which is characteristic of pyrogen reactions.

Room temperatures were recorded (wet and dry bulb) using a Taylor Humidiguide thermometer. The wet bulb temperature was adopted as the more significant (3). The wet bulb temperature varied from 50 to 78F., with an average of 62.3 F. Rectal temperatures were recorded immediately before and after anesthesia, using a U. S. Bureau of Standards clinical thermometer, except in cases where continuous temperatures were taken with a Yellow Springs Instrument Company's "Telethermometer." Studies of skin temperatures were made with a McKesson Dermalor apparatus. In all cases patients were observed for 15 minutes following termination of anesthesia. During this time they were uncovered and fully exposed to room atmosphere. Careful note was made of the plane of anesthesia during this time.

In such a clinical study it was difficult to exclude many variable factors. All types of operations were included; and the size of the wound, blood replacement and skin exposure were but a few of the conditions which varied considerably. For this reason this investigation is to be taken as a scout study and the data will be used only for general deductions.

RESULTS

Incidence of Post-anesthetic Tremor.—Of 120 patients anesthetized with thiopental, 78 (55 per cent) showed characteristic tremor; of 120 patients anesthetized with ether 38 (31.7 per cent) showed tremor; and

in a smaller series of 20 patients anesthetized with cyclopropane, 5 (25 per cent) showed tremor (table 1).

These figures give a baseline for the incidence of shivering for children anesthetized with thiopental, ether, and cyclopropane in a cool environment. The data demonstrate an appreciable incidence of shivering with all three agents, but a marked preponderance in those who received thiopental.

Character of Tremor.—The type of tremor following anesthesia was similar regardless of the agent used. The severity varied considerably with all agents. The tremor in the mildest form usually began with fibrillary contraction of masseters, which might have escaped notice unless under special scrutiny. In more pronounced development the tremor would spread to involve the head, shoulders, trunk and limbs in the form of fine, rapid shaking. This never simulated the coarse contractions of a convulsion and no twitchings about the mouth or eyes were observed. The tremors lasted from a few moments to 30 minutes or more. When sufficiently conscious, patients often showed gooseflesh and complained of feeling cold. This tremor

TABLE 1
GROSS INCIDENCE OF SHIVERING

Anesthetic	Did Not Shiver	Shivered	Total	% Shivered
Thiopental	42	78	120	65.0
Ether	82	38	120	31.7
Cyclopropane	15	5	20	25.0

to us simulated in every way that of true thermal shivering and, for that reason, we feel that the term "shivering" should supplant less definitive terms such as "shakes" or "tremor."

Plane of Anesthesia During Shivering.—Note was made of the plane of anesthesia during the postoperative period of observation. All patients who shivered were in a light plane of anesthesia, as shown by their reaction to pain, the presence of patellar reflexes, or a return of consciousness. No patients who were still in surgical anesthesia showed evidence of shivering. Of 120 patients anesthetized with thiopental, only 2 remained deeply anesthetized throughout the fifteen minute postoperative observation period, while 23 of the 120 etherized patients remained deeply anesthetized. All patients under cyclopropane recovered reflexes during the observation period. One rather obvious factor is demonstrated: more patients will shiver following thiopental than following ether because they more frequently awaken in the immediate post-anesthetic period when they are most likely to be exposed. The statistics were therefore revised to include only those patients who were in a plane of anesthesia light enough to allow shivering during the observation period (table 2).

TABLE 2
INCIDENCE OF SHIVERING IN PATIENTS IN A LIGHT PLANE OF ANESTHESIA

Anesthetic	Did Not Shiver	Shivered	Total	% Shivered
Thiopental	40	78	118	66.1
Ether	59	38	97	39.2
Cyclopropane	15	5	20	25.0

Heat Loss During Anesthesia.—Shivering following thiopental has been ascribed to greater heat loss under this agent. A normal subject loses heat through conduction, convection, vaporization and radiation but he balances this loss by heat production (4). Most anesthetic agents upset this balance by decreasing muscle activity and causing peripheral vasodilatation, whereas surgery adds further to heat loss through chilling skin disinfectants, wounds of varied dimensions, infusions of iced blood and so on.

The relative effect of different anesthetics is hard to determine. Two explanations for greater cooling under thiopental might be offered: [1] the increased blood volume associated with thiopental anesthesia (5) might facilitate heat loss through the skin; [2] as noted by Rochberg and Apgar (6), and by Clark and Orkin (3), large ventilatory heat losses can occur with use of open or semiclosed techniques. Since thiopental is customarily used with semiclosed supplementation and cyclopropane only with closed techniques this might account for considerably greater heat losses under thiopental.

Our figures, however, fail to show any preponderant tendency to lose heat under thiopental. When patients shivered following thiopental, ether, or cyclopropane anesthesia the average fall in body temperature was 1.35, 2.6 and 1.2 F., respectively, ether showing the greatest loss (table 3).

The maximum heat loss of 5.2 F. under thiopental was matched by a similar loss under ether. It is to be noted that one patient shivered after thiopental even in the presence of a 1.0 degree gain in temperature. This did not happen with the other agents. [Jung has

TABLE 3
CHANGES IN BODY HEAT
(Patients Who Shivered)

		Thiopental (78)*	Ether (38)*	Cyclopropane (5)*
Rectal temp., ° F.	Max. gain	+1.0	-1.0	-0.2
	Av. loss	-1.35	-2.6	-1.2
	Max. loss	-5.2	-5.2	-3.5

* Number of patients.

shown that, in normal subjects, shivering can occur in presence of elevated body temperature (7)]. Data on patients who did not shiver showed that both the average heat losses and maximum heat losses were greater following ether and cyclopropane than those following thiopental (table 4).

These figures suggest that the underlying factor is *not greater heat loss* under thiopental, but an *increased sensitivity to cold* with this agent. In other words, patients do not shiver because they have lost an excessive amount of heat, but because the shivering mechanism is more easily evoked under the same conditions. This is borne out by the observation that, following thiopental anesthesia, no patients failed to shiver who had lost more than 1.4 F., while patients awoke from ether and cyclopropane having lost 3.4 degrees and still did not shiver.

Relationship of Room Temperature to Shivering.—The room temperatures in this study varied from 50 F. to 78 F., WBT, with an average of 62.3 F. Room temperatures in the case of both shivering and nonshivering patients varied widely and there was considerable over-

TABLE 4
CHANGES IN BODY HEAT
(Patients Who Did Not Shiver)

		Thiopental	Ether	Cyclopropane
Rectal temp., ° F.	Max. gain	+1.4	+2.6	+1.0
	Av. loss	-0.4	-1.2	-0.9
	Max. loss	-1.4	-3.4	-3.4

lapping, some patients shivering at relatively warm room temperatures while others failed to shiver in much cooler surroundings (figure 1). This is understandable because there were other variables and in view of differences in the tendency to shiver between individuals. It was apparent with all agents, however, that the incidence of shivering increased at colder room temperatures. The average room temperature in cases of shivering patients was definitely lower than in nonshivering patients with all agents. The increased tendency to shiver with thiopental is shown by the occurrence of shivering at higher average room temperatures than with either ether or cyclopropane. Furthermore, individual patients shivered in rooms as warm as 74 F. following thiopental, whereas the highest room temperatures at which patients shivered following ether or cyclopropane were 68 and 64 F., respectively. It can therefore be deduced that room temperature is an important contributing factor in the etiology of shivering with all agents, and that it helps to demonstrate a greater sensitivity to cold in patients who have had thiopental-nitrous oxide-oxygen anesthesia.

Relation of Skin Temperature To Shivering.—Cooling of surface

TABLE 5
ACID-BASE BALANCE
(Thiopental Anesthesia)

Shivered		Did Not Shiver	
pH	CO ₂	pH	CO ₂
1. 7.40	28.3 mEq./L.	8. 7.30	31.2 mEq./L.
2. 7.42	28.7 mEq./L.	9. 7.33	27.1 mEq./L.
3. 7.46	26.8 mEq./L.	10. 7.43	25.7 mEq./L.
4. 7.39	36.1 mEq./L.	11. 7.27	25.8 mEq./L.
5. 7.37	25.8 mEq./L.	Av. 7.33	Av. 27.5 mEq./L.
6. 7.40	26.5 mEq./L.		
7. 7.40	28.3 mEq./L.		
Av. 7.41	Av. 28.7 mEq./L.		

Because temperature regulation is known to be incompletely developed in early infancy (11), patients under 6 months of age were excluded from the statistics of this study. However, two observations were of interest: [1] several infants were observed to shiver though less than 1 month of age, and [2] body temperatures of infants were observed to fall as low as 88.5 F. by rectum without intentional use of refrigeration techniques. This and other excessive temperature losses occurred in small infants under endotracheal Y-tube ether insufflation.

The Role of Carbon Dioxide.—The belief has been voiced that carbon dioxide retention might underlie thiopental shivering. In our

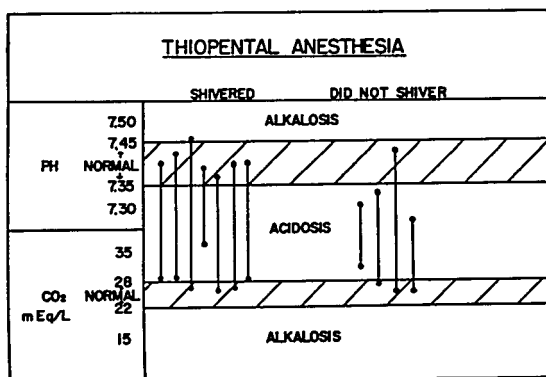


FIG. 2. Acid-base balance in thiopental anesthesia. CO₂ and pH in 7 cases of patients who shivered and 4 who did not.

experience it seemed more probable that with assisted semiclosed technique hyperventilation might occur, blowing off sufficient carbon dioxide to lead toward the hyperirritable state of alkalotic tetany (12). Accordingly, arterial carbon dioxide and pH levels were determined in 11 cases shortly before termination of thiopental anesthesia. Seven patients subsequently shivered; 4 did not. Carbon dioxide levels in both groups proved slightly on the acidotic side of normal (table 5 and fig. 2). The pH in all 7 cases of shivering patients, however, was normal or alkalotic, whereas in 3 of the 4 nonshivering group there was a definitely lowered or acidotic pH. These findings do not support the contention that thiopental shivering is related to carbon dioxide excess or to hypocarbia.

Cortical Activity Following Thiopental.—Increased reflex irritability is reported in light thiopental anesthesia (13, 14). Since shivering is a reflex under hypothalamic and cortical control (15), it seemed reasonable to look for evidence of increased cortical activity as a factor in thiopental shivering. Electro-encephalographic studies were made on three different occasions on one subject undergoing thiopental anesthesia without surgery. In two instances shivering occurred; in the third there was none. Encephalographic activity was followed continuously from the preanesthetic period until full consciousness had been regained. In no instance was there any electro-encephalographic evidence of increased cortical activity.

COMMENT

Adrenal Activity and Glycogen Metabolism.—The adrenals play a significant part in stimulating heat production by liberating glycogen from liver and muscles (16). Cannon (17) held that adrenal activity was the first line of defense against cold, and showed that sympathectomized animals shivered excessively when exposed to low temperatures. Furthermore, the injection of epinephrine has been demonstrated to arrest shivering (18).

Evidence that thiopental depresses adrenal activity is observed clinically in constricted pupils and a lowered pulse rate and blood pressure in anesthetized patients, and Campbell and Morgan (10) have reported experimental evidence of adrenal suppression by barbiturates. The work of Booker (19, 20), showing depression of glycogen metabolism by thiopental, and that of Langlois and Williams (21), showing prolongation of thiopental narcosis by glucose administration, give further proof of the important effect of barbiturates on adrenal physiology.

With these considerations in mind, the possibility is strongly suggested that adrenal suppression might be the underlying factor in thiopental shivering. It is to be remembered however, that patients have not been observed to shiver noticeably after spinal anesthesia,

with its associated adrenal blockade, and we are left with the belief that adrenal depression may be an important but contributory factor in thiopental shivering.

Significance of Shivering.—It should be pointed out that, regardless of its cause, shivering may have a definitely harmful effect. Owing to the increased muscular activity involved, oxygen demand may be increased 200–400 per cent (22). This may be of great danger to patients following operation for cyanotic heart disease, or to others with poor cardiorespiratory reserve. With the greater use of air conditioning and induced hypothermia, this will be of increasing importance.

SUMMARY

A series of 259 children were anesthetized with thiopental, ether or cyclopropane in air-conditioned operating rooms.

Post-anesthetic tremors occurred in a significant number of cases following both ether and cyclopropane anesthesia, but in a far greater number after thiopental.

Such tremors are believed to represent true thermal shivering.

After an attempt to eliminate pyrogens, other possible causes of thiopental shivering were examined.

No evidence of carbon dioxide excess or increased cortical irritability was found in shivering patients.

Central and surface temperature changes under thiopental anesthesia did not suggest any significant depression of temperature regulating mechanisms.

An increased sensitivity to cold following thiopental nitrous oxide-oxygen anesthesia was suggested by observation of shivering in warmer rooms, and with less heat loss than after ether or cyclopropane.

Many factors were found which probably play contributing roles in thiopental shivering. These include large ventilatory heat loss, adrenal suppression, early awakening, and rapid return of the shivering reflex.

Note is made of the harmful effect of shivering in “poor risk” patients.

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