

## TECHNICAL PROBLEMS OF STUDYING INTRAVENOUS ANESTHETICS IN MAN

LT. COMDR. LAWRENCE D. EGBERT, USN (MC)

LT. COMDR. GEORGE D. MITCHELL, USN (MC)

INVESTIGATIONS with intravenous barbiturates have shown large differences between subjects in the onset and duration of hypnosis. Variation in the results from any clinical experiment may be caused by differences in the drugs studied, in the subjects used, and in the experimental design. Most studies of intravenous barbiturates have not adequately controlled the technical factors involved in injecting drugs and in measuring their subjective effects upon patients. This belief prompted us to investigate the effects upon the onset and duration of hypnosis with thiopental by varying the rate and site of injection and by varying the concentration.

### METHODS

We used two methods. First, we measured the times of onset and duration of hypnosis after thiopental when four different techniques of intravenous injection were used (table 1). The rate of injection, concentration of drug, and location of the needle were selected in random order. Second, we compared the onset and duration of hypnosis with 2.5 and 3.5 per cent thiopental with a double-blind technique. The unknown solution, consisting of either 2.5 or 3.5 per cent thiopental, was given 1 ml. every five seconds until the patient slept.

One hundred eighteen healthy women were studied just before induction of anesthesia for minor gynecologic operations. Several women stopped breathing for a short time or had obstruction of the upper airway after the injection. Data were not obtained from three patients because of respiratory obstruction. The 115 patients presented here did not receive artificial respiration. Atropine, 0.4 mg., was administered intramuscularly about one hour before beginning the studies.

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The patients were made as comfortable as possible, lying supine on an operating table. As the injection was begun, a stopwatch was started, and the patients were asked to count backwards from 100. They were considered asleep when they stopped counting. No external stimuli were permitted during the period of hypnosis. We repeatedly asked the patients to start counting again and judged the hypnosis ended when they obeyed.

### RESULTS

The differences between group averages in age, height, weight, and hemoglobin concentration were not statistically significant (tables 1 and 2).

As shown by the standard deviations in table 1, the onset of hypnosis was fairly consistent from patient to patient; the duration was more variable. The onset after a slow rate of injection was delayed compared to the onset after a more rapid injection (technique 2 compared with technique 1, table 1,  $P < 0.1$ ). The difference in time of onset of hypnosis between 3.5 and 2.5 per cent thiopental was not statistically significant (technique 3 compared with 1). Injection into the veins on the back of the hand probably delayed the onset of hypnosis (technique 4 compared with 1, questionable significance,  $.05 < P < 0.1$ ). The duration of hypnosis was significantly longer ( $P < .01$ ) after 8 ml. of 3.5 per cent thiopental than after 8 ml. of 2.5 per cent thiopental. Varying the rate of injection or the location of the needle did not significantly alter the duration of hypnosis.

When 2.5 and 3.5 per cent thiopental were injected at a constant rate until the patients slept, the dose, in milliliters, of 3.5 per cent thiopental was significantly ( $P < .01$ ) less than the dose of 2.5 per cent thiopental (table 2); in milligrams, however, the dose of 3.5 per cent thiopental was significantly greater ( $P < 0.1$ ). The duration of hypnosis

TABLE 1

THE EFFECT OF DIFFERENT METHODS OF INJECTION UPON THE ONSET AND DURATION  
OF THIOPENTAL HYPNOSIS

Technique*	No. Patients	Age (years)		Height (inches)		Weight (pounds)		Hemoglobin (Gm. %)		Onset (seconds)		Duration (seconds)	
		Mean	S.D.†	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
1	16	34.6 ± 10.6		63.3 ± 2.5		126.3 ± 20.7		12.6 ± 1.4		37.8 ± 8.8		182.5 ± 151.5	
2	14	35.7 ± 13.5		64.0 ± 3.0		137.5 ± 30.1		12.8 ± 1.0		62.3 ± 11.7		248.0 ± 271.0	
3	17	30.0 ± 7.4		65.0 ± 2.5		129.8 ± 26.4		12.5 ± 0.8		33.6 ± 5.5		642.5 ± 492.0	
4	14	32.5 ± 10.0		63.6 ± 3.0		131.2 ± 38.0		12.3 ± 1.3		43.7 ± 8.9		228.8 ± 148.0	

\* Techniques:

1. 200 mg. (8 ml. 2.5 per cent) thiopental into antecubital vein, 1 ml. per 5 seconds.
2. 200 mg. (8 ml. 2.5 per cent) thiopental into antecubital vein, 1 ml. per 10 seconds.
3. 280 mg. (8 ml. 3.5 per cent) thiopental into antecubital vein, 1 ml. per 5 seconds.
4. 200 mg. (8 ml. 2.5 per cent) thiopental in vein on dorsum of hand, 1 ml. per 5 seconds.

† Standard Deviation.

TABLE 2

COMPARISON OF 2.5 AND 3.5 PER CENT THIOPENTAL ADMINISTERED WITH SIMILAR TECHNIQUE

Dose Thiopental (%)	No. Patients	Age (years)		Height (inches)		Weight (pounds)		Hemoglobin (Gm. %)		Dose (ml.)		Dose (mg.)		Duration (seconds)	
		Mean	S.D.*	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
2.5	24	32.1 ± 9.8		63.5 ± 3.6		130 ± 22		12.8 ± 1.2		7.67 ± 1.17		192 ± 29.2		202.5 ± 161	
3.5	30	33.8 ± 9.3		63.1 ± 2.9		129 ± 21		13.0 ± 1.1		6.85 ± 0.87		240 ± 51.6		310.5 ± 212	

\* Standard Deviation.

was longer after administration of 3.5 per cent thiopental ( $P < .05$ ).

## DISCUSSION

In any study of a new drug, comparison with a familiar and relatively standardized drug is a most informative approach. In a properly planned experiment sources of variation must act equally upon both drugs.<sup>1</sup>

The data from our first group of patients suggest the importance of standardizing the rate and location of injection and the concentration of the drugs studied. Dundee<sup>2</sup> mentions the importance of a constant rate of injection. Most published reports about new intravenous anesthetic agents, however, do not describe adequately the technique of their administration. Our second group of studies corroborates the need for an accurate estimation of the relative potency of two drugs before attempting to compare the duration of action. Since we administered a

smaller volume of 3.5 per cent thiopental than 2.5 per cent thiopental, the average dose in milligrams should have been about the same with either drug. The significantly greater dose in milligrams and the longer duration of hypnosis with 3.5 per cent thiopental prove that our definition of the onset of hypnosis was not accurate enough to determine the difference in onset between 2.5 and 3.5 per cent thiopental. Although the electroencephalogram has been thought a more accurate method of measuring the action of intravenous barbiturates,<sup>3</sup> Brazier and Beecher<sup>4</sup> were not able to distinguish a placebo from pentobarbital, 90 mg., by this method.

Despite standardization of technique, our results varied considerably. Other factors which affect the duration of intravenous barbiturates are:

(1) The environment<sup>2</sup> and psychologic state of patients.<sup>3</sup> Patients sleep longer in a

quiet, unstimulating, comfortable situation than in a noisy or uncomfortable place. The patients' physical and psychologic condition is difficult to control in an operating room.

(2) The age, sex, and weight of the patients.<sup>5, 6</sup> Statistical randomization of the order of the treatments will neutralize these variables.<sup>1</sup>

(3) Previous administration of other central nervous system depressants.<sup>7</sup> Tolerance to barbiturates, however, may develop rapidly.<sup>2, 8</sup> Probably ideally, patients who have received sedatives within a week before the study should not be included in a clinical investigation of intravenous barbiturates.

(4) The pattern of distribution and detoxification in the body.<sup>8, 9</sup> Varying blood flow to fat and to muscle may alter the duration of hypnosis in the same patient from time to time. For example, patients with anemia<sup>10</sup> and patients in shock<sup>11</sup> are more susceptible to intravenous barbiturates than are normal patients.

(5) Altering the pattern of respiration.<sup>12</sup> Respiratory depression would have confused our results if the depression was longer with 3.5 per cent thiopental than with 2.5 per cent thiopental. We did not assist respiration for any of our patients because we wished to avoid the physical stimulation of a mask. Apnea did not last longer than one minute in any patient, so that blood oxygen and carbon dioxide concentrations were probably close to normal.

#### CONCLUSIONS

After studying the times of onset and termination of thiopental hypnosis following different techniques of administration, we found that:

Decreasing the rate of injection delays the onset of hypnosis. Changing the site of injection probably changes the time of onset of hypnosis. Thiopental, 3.5 per cent, does not cause subjects to go to sleep rapidly enough to be differentiated experimentally from 2.5 per cent thiopental.

Proper investigation of a new intravenous anesthetic agent must consider the rate and site of injection; a comparison of the potency of a new drug with a standard drug should be done before comparison of their durations of action.

Our statements do not necessarily represent the opinion of the Navy Department.

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