

## Decreased Thiopental Requirements in Early Pregnancy

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**Background:** Anesthetic requirements for inhalational agents are decreased during pregnancy, but there are no data regarding requirements for intravenous agents. The quantal dose-response curves for thiopental were calculated for 70 nonpregnant women having gynecologic surgery and for 70 pregnant women of 7-13 weeks' gestation having elective abortions.

**Methods:** Groups of 10 patients were given 2, 2.4, 2.8, 3.3, 3.8, 4.5, or 5.3 mg/kg thiopental as a bolus dose during a period of 10 s. Two minutes later, patients were asked to open their eyes as a test for hypnosis. Patients who did not open their eyes were given a 10-s, 50-Hz, 80-mA transcutaneous tetanic electrical stimulus to the ulnar nerve as a test for anesthesia. Purposeful movement indicated that there was no anesthesia. Log dose-response curves for hypnosis and anesthesia were calculated after logit transformation.

**Results:** In the nonpregnant women, the median effective doses (ED<sub>50</sub>s) (95% confidence interval) for hypnosis and anesthesia were 3.1 (2.8-3.4) mg/kg and 4.9 (4.5-5.4) mg/kg, whereas in the pregnant women the corresponding ED<sub>50</sub>s were 2.6 (2.3-2.8) mg/kg and 4 (3.7-4.4) mg/kg. In the nonpregnant women, the ED<sub>95</sub>s (95% CI) for hypnosis and anesthesia were 4.4 (3.9-5.4) mg/kg and 6.4 (5.7-7.9) mg/kg, whereas in the pregnant women the corresponding ED<sub>95</sub>s were 3.7 (3.3-4.5) mg/kg and 5.2 (4.7-6.3) mg/kg. The pregnant to nonpregnant relative median potency (95% CI) ratio for hypnosis was 0.83 (0.67-0.96) and for anesthesia it was 0.82 (0.62-0.94).

**Conclusions:** The dose of thiopental for hypnosis was 17% less and that for anesthesia was 18% less in pregnant women of 7-13 weeks' gestation compared with that in nonpregnant

women. (Key words: Anesthesia: obstetric. Anesthetics, intravenous: thiopental. Potency: induction; lean body mass.)

WE recently showed that the minimum alveolar concentration (MAC) for isoflurane in pregnant women of 8-12 weeks' gestation (0.775 vol%) was less than the MAC obtained in nonpregnant women (1.075 vol%).<sup>1</sup> This was the first human study to confirm earlier animal work showing reduced MAC in pregnant ewes<sup>2</sup> and pregnant rats.<sup>3</sup> However, no animal or human data exist regarding the requirements for intravenous anesthetics during pregnancy.

Thus we wanted to determine whether pregnant patients needed less thiopental for anesthesia. We tested this hypothesis by comparing the quantal dose-response curves, using end points of hypnosis and anesthesia, after a bolus dose of thiopental was administered to patients having elective abortions at 7-13 weeks' gestation, and in nonpregnant women having elective gynecologic surgery.

### Materials and Methods

The study was approved by the local clinical research ethics committee and 70 pregnant and 70 nonpregnant patients were recruited. Patients were eligible for the study if they were classified as American Society of Anesthesiologists (ASA) physical status 1, ages 16-45 y, and had no known contraindication to using thiopental. Patients were excluded if they were postmenopausal, or taking any medications, including oral contraceptives. Pregnant patients had a positive result on pregnancy testing, ultrasonic confirmation of pregnancy, and were of 7-13 weeks' gestation and scheduled for abortion. Nonpregnant patients had a negative result on pregnancy testing, reported menstruation in the previous 5 weeks, and were scheduled for gynecologic surgery. Written informed consent was obtained from all patients.

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Patients in each group were subdivided into seven sets of 10 patients, each set to receive a fixed dose of thiopental. The seven doses of thiopental, 2, 2.4, 2.8, 3.3, 3.8, 4.5, and 5.3 mg/kg, were derived from our previous experience with this technique,<sup>4</sup> and the logarithms of the doses were approximately equally spaced. Patients were allocated in a double-blinded manner to a particular dose by using shuffled, sealed envelopes. Thiopental 2.5% was prepared in a double-blinded manner and diluted with sterile water to a final volume of 20 ml. Although it was intended that the observers were to be blinded to the study group, this was not always possible because of admission procedures beyond our control. Most patients scheduled for abortion were scheduled for operation on Tuesday. Thus it was likely that any patient studied on that day was pregnant, whereas a patient studied on any other day was likely to be nonpregnant. Nevertheless, we believe that the standardization of the method, well-defined end points, and the presence of several nurse observers would have minimized any bias.

No premedication was given. Arterial pressure was recorded noninvasively by the automated module in a Narkomed 4E anesthetic machine (North American Dräger, Telford, PA). Timed by stopwatch, the thiopental was injected over a period of 10 s and followed by a further 10-ml dose of physiologic saline. The patient was undisturbed except for the noninvasive recording of arterial pressure. Systolic, mean, and diastolic arterial pressure and heart rate were recorded immediately before injection of thiopental, at 1 min, and at 2 min.

Two minutes after the start of the thiopental injection, the patient was called by her name and asked to open her eyes. Patients who opened their eyes were recorded as not being hypnotized. Patients who did not open their eyes were recorded as hypnotized and were given a 50-Hz, 80-mA transcutaneous tetanic stimulus to the ulnar nerve at the wrist delivered in 200- $\mu$ s pulses by a constant-current peripheral nerve stimulator (NS252; Fisher & Paykel Healthcare, Auckland, New Zealand). This machine delivers a monophasic, unidirectional square wave with a rising time of less than 5  $\mu$ s, has a maximum output of 350 V, and will alarm if the current is more than 5 mA different from that selected. The stimulus was given for 10 s or until there was purposeful movement in one of the nonstimulated limbs during the tetanus.<sup>5</sup> This was considered a positive response and the patient was recorded as not being anesthetized. Swallowing, grimacing, hyperventilation, and coughing

were not considered positive responses. Patients who were recorded as not being hypnotized were not given the tetanic stimulus and thus were recorded as not being anesthetized. The investigator who assessed hypnosis and anesthesia was blinded to the dose of thiopental.

Statistical analysis was performed using SPSS 6.1 (SPSS Ltd., Chicago, IL) running on a Macintosh Quadra 650 computer (Apple Computers, Cupertino, CA). Demographic data were compared between groups using the Mann-Whitney test, and logistic regression was used to identify significant factors affecting thiopental requirement. Quantal log dose-response curves were calculated and compared using the advanced statistics probit analysis module with logit transformation of data. Data were also reanalyzed by the same method after recalculating each patient's dose of thiopental based on her lean body mass. Lean body mass was calculated using the formula:

$$\text{lean body mass} = 1.07 (\text{total body weight}) - 148 (\text{total body weight/height})^2$$

where lean body mass and total body weight are measured in kilograms and height is measured in centimeters.<sup>6</sup> The percentage changes in arterial pressure and heart rate from 0 to 1 min and from 0 to 2 min were analyzed by multiple regression using log dose and patient group as independent variables. Probability values less than 0.05 were considered significant.

## Results

On postoperative review, six patients were discovered to have violated the inclusion criteria. One patient had abnormal thyroid function test results that were not available before operation, one patient had diabetes mellitus controlled by diet, one patient had taken an unknown Chinese herbal medicine before operation, two patients had been taking oral contraceptive pills irregularly, and one patient had received a recent course of clomiphene. Another patient had an 8-kg ovarian tumor removed at operation, casting doubt that she received the appropriate dosage of thiopental calculated by body weight. Data for these patients were replaced.

Demographic characteristics (median [range]) for nonpregnant patients included age, 34 y (18–42 y); weight, 54 kg (38–74 kg); lean body mass, 39.5 kg (31.7–51.3 kg); and height, 1.53 m (1.44–1.72 m). Cor-



## THIOPENTAL REQUIREMENTS IN PREGNANCY

**Table 1. Number of Patients (of a Total of 10) with Hypnosis and Anesthesia at Different Doses of Thiopental**

Dose (mg · kg <sup>-1</sup> )	Hypnosis		Anesthesia	
	Nonpregnant	Pregnant	Nonpregnant	Pregnant
2.0	0	1	0	0
2.4	1	5	0	0
2.8	4	6	0	0
3.3	7	8	0	0
3.8	7	10	0	5
4.5	10	10	3	8
5.3	10	10	7	9

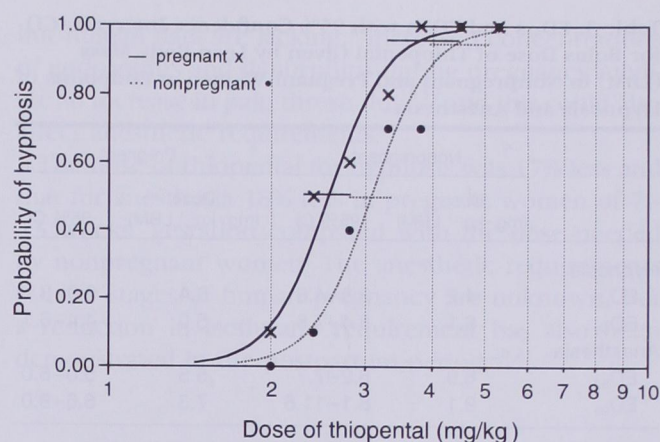
responding data in pregnant patients were age, 27 y (16–43 y), weight, 54 kg (39–76 kg); lean body mass, 39.5 kg (31.3–48.4 kg); and height 1.55 m (1.40–1.67 m). Nonpregnant patients were older than pregnant patients ( $P < 0.01$ ), but weight, lean body mass, and height were similar for the two groups. The pregnant patients were 11 (range, 7–13) weeks pregnant by dates, and pathologic examination confirmed products of conception from all women. Logistic regression identified pregnancy and thiopental dose, but not age, as significant independent variables affecting thiopental requirement.

The patients' responses at end points of hypnosis and anesthesia are presented in table 1, and derived ED<sub>50</sub>s and ED<sub>95</sub>s are shown in table 2. The calculated log dose-response curves are shown in figures 1 and 2. The pregnant-to-nonpregnant relative median potency (95% CI) for hypnosis was 0.83 (0.67–0.96) and for anesthesia it was 0.82 (0.62–0.94).

A similar reduction in dose requirement was found

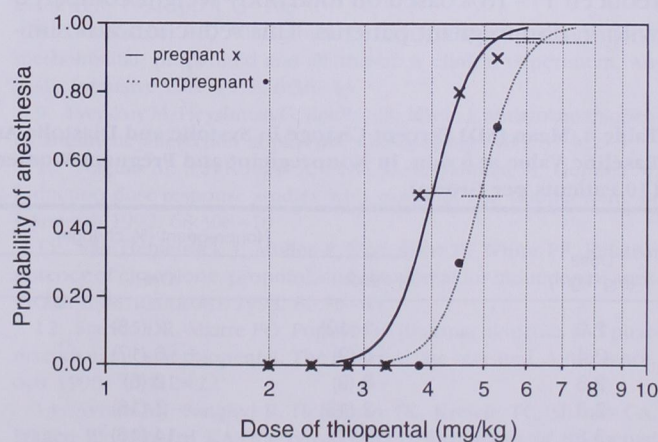
**Table 2. ED<sub>50</sub>s and ED<sub>95</sub>s with 95% Confidence Intervals (CI) for Bolus Dose of Thiopental Given by Total Body Weight in Nonpregnant and Pregnant Women at Endpoints of Hypnosis and Anesthesia**

	Nonpregnant		Pregnant	
	Dose (mg · kg <sup>-1</sup> )	95% CI	Dose (mg · kg <sup>-1</sup> )	95% CI
Hypnosis				
ED <sub>50</sub>	3.1	2.8–3.4	2.6	2.3–2.8
ED <sub>95</sub>	4.4	3.9–5.4	3.7	3.3–4.5
Anesthesia				
ED <sub>50</sub>	4.9	4.5–5.4	4.0	3.7–4.4
ED <sub>95</sub>	6.4	5.7–7.9	5.2	4.7–6.3

**Fig. 1. Calculated dose-response curves (log dose scale) for hypnosis in pregnant and nonpregnant women. The 95% confidence intervals for the ED<sub>50</sub>s and ED<sub>95</sub>s are also displayed, slightly offset for clarity. Raw data shown by x (pregnant group) and • (nonpregnant group).**

when the thiopental dose was recalculated using the patients' lean body mass (table 3). Comparison of the log dose-response curves based on lean body mass revealed a pregnant-to-nonpregnant relative median potency (95% CI) for hypnosis of 0.81 (0.62–0.94) and that for anesthesia of 0.80 (0.60–0.93).

Baseline systolic and diastolic arterial pressure were greater in the nonpregnant women, at a mean (SD) of 120 (14) mmHg and 70 (9) mmHg, than in the pregnant

**Fig. 2. Calculated dose-response curves (log dose scale) for anesthesia in pregnant and nonpregnant women. The 95% confidence intervals for the ED<sub>50</sub>s and ED<sub>95</sub>s are also displayed, slightly offset for clarity. Raw data shown by x (pregnant group) and • (nonpregnant group).**



**Table 3. ED<sub>50</sub>s and ED<sub>95</sub>s with 95% Confidence Intervals (CI) for Bolus Dose of Thiopental Given by Lean Body Mass (LBM) in Nonpregnant and Pregnant Women at Endpoints of Hypnosis and Anesthesia**

	Nonpregnant		Pregnant	
	Dose (mg · kg <sup>-1</sup> LBM)	95% CI	Dose (mg · kg <sup>-1</sup> LBM)	95% CI
Hypnosis				
ED <sub>50</sub>	4.2	3.8–4.6	3.4	3.0–3.7
ED <sub>95</sub>	6.1	5.4–7.6	5.0	4.4–6.1
Anesthesia				
ED <sub>50</sub>	6.9	6.2–7.7	5.5	5.0–6.0
ED <sub>95</sub>	9.1	8.1–11.6	7.3	6.6–9.0

women at 115 (12) mmHg ( $P < 0.05$ ) and 62 (10) mmHg ( $P < 0.001$ ). Baseline heart rate in the nonpregnant women, 80 (13) bpm was similar to that in the pregnant women at 80 (13) bpm. Increasing thiopental dose was associated with a greater percentage increase in heart rate at 2 min compared with baseline values for both groups ( $P < 0.05$ ; table 4). There was no significant regression between thiopental dose and changes in arterial pressure. Changes in arterial pressure and heart rate were not different between pregnant and nonpregnant groups.

## Discussion

In pregnant patients, the thiopental requirement is reduced 17–18% based on total body weight compared with in nonpregnant patients. This reduction was simi-

lar (19–20%) when recalculating the dose of thiopental according to lean body mass. Although drug dosing by lean body mass can reduce variability in observed response,<sup>6</sup> it is uncertain how this can be applied to the weight gain seen in pregnancy. In any case, the weight gain before 13 weeks' gestation is usually less than 1 kg,<sup>7</sup> and there were no differences in patient weight between the groups.

Our estimates of ED<sub>50</sub> and ED<sub>95</sub> in unpremedicated nonpregnant women are comparable to those found in previous studies.<sup>4,8–11</sup> Any differences in ED<sub>50</sub> can be attributed to variation among studies in the method of determining the end point, the timing of assessment, and the use of premedication.

The estimates of ED<sub>95</sub>s have wider confidence intervals than those for the ED<sub>50</sub>s, and the extrapolated ED<sub>95</sub> for anesthesia in the nonpregnant women (6.4 mg/kg) was outside the dose range of thiopental used. Our extrapolation relies on the assumption that the thiopental log dose-response relationship is sigmoid in shape, and this has been an appropriate model in previous studies.<sup>12,13</sup> Although there are various sigmoid functions, it is not obvious that any one is superior for curve fitting, and the results from probit or logit models are almost identical. Nevertheless, one should be cautious in interpreting the ED<sub>95</sub>s, and their wide confidence intervals reflect the limitations of these estimates.

We used two clinical end points, and although loss of patient response to verbal command is familiar to all anesthetists, the clinical significance of loss of response to tetanic electrical stimulus may be unfamiliar to some. Zbinden and coworkers<sup>5</sup> evaluated and discussed multi-

**Table 4. Mean (SD) Percent Change in Systolic and Diastolic Arterial Pressure (SAP, DAP) and Heart Rate (HR) at 2 min Versus Baseline Value at 0 min, in Nonpregnant and Pregnant Women Receiving Various Dosages of Thiopental (10 Patients per Group)**

Dose (mg · kg <sup>-1</sup> )	Nonpregnant (% change)			Pregnant (% change)		
	SAP	DAP	HR	SAP	DAP	HR
2.0	-1 (10)	2 (18)	6 (15)	-7 (6)	0 (17)	0 (17)
2.4	-8 (9)	-6 (17)	3 (10)	-3 (9)	-11 (9)	3 (15)
2.8	-8 (9)	-12 (6)	4 (13)	-3 (6)	6 (25)	9 (15)
3.3	-2 (13)	-7 (16)	4 (14)	-9 (7)	-17 (12)	3 (14)
3.8	-10 (7)	-14 (16)	4 (20)	-6 (12)	-3 (18)	24 (28)
4.5	-8 (10)	-18 (17)	14 (26)	-10 (16)	-5 (17)	13 (20)
5.3	-9 (6)	-4 (20)	12 (19)	-10 (10)	2 (26)	10 (15)

Multiple regression showed a significant increase in HR with increasing log dose of thiopental ( $P < 0.05$ ) but no other differences in SAP or DAP with dose, and no differences between nonpregnant and pregnant groups.



## THIOPENTAL REQUIREMENTS IN PREGNANCY

ple noxious stimuli during isoflurane anesthesia. The MAC of isoflurane required to suppress somatic movement to a tetanic electrical stimulus (1.03%) was similar to that required for laryngoscopy (1%) and skin incision (1.16%).

The difference in thiopental requirement may be a result of pharmacodynamic or pharmacokinetic differences between pregnant and nonpregnant women. In a previous study with isoflurane,<sup>1</sup> at least a pharmacodynamic difference was observed for inhalational agents between pregnant and nonpregnant women. The reduction in isoflurane concentration (median [95% CI]) of 33% (28–37%) was estimated more precisely than the reduction in thiopental dose at 18% (6–38%). This partly reflects the different methods used in the studies; one designed to maintain stable effect-site concentrations of isoflurane and the other using set doses of thiopental with some inevitable variation in effect-site concentrations.

There may be differences in pharmacokinetics between pregnant and nonpregnant patients so that after the same induction dose of thiopental, the effect-site concentrations of thiopental may be different between groups at the time of testing for hypnosis and anesthesia. For example, cardiac output is increased by 20% at 13 weeks' gestation and the regional distribution of blood flow is altered, with cerebral blood flow being a smaller proportion of cardiac output.<sup>14</sup> Thus a smaller proportion of the initial bolus thiopental dose may reach the effect site in pregnant women. These confounding factors can only be eliminated by maintaining stable effect-site concentrations of the intravenous agent, and a study using computer-controlled infusions of propofol is in progress.

The concentration of albumin is reduced by approximately 10% at the end of the first trimester, and reduced protein binding of thiopental may have influenced our results. However, although there are no data on the changes in protein binding of thiopental in early pregnancy, protein binding was unchanged in full-term pregnant patients, who have even lower albumin concentrations.<sup>15</sup>

The underlying mechanism for the decreased anesthetic requirements during pregnancy is unclear. Progesterone can reduce anesthetic requirements in animals,<sup>16,17</sup>

but human data are lacking.<sup>1</sup> Increased concentrations of endorphins and dynorphins during pregnancy mediate an increase in pain threshold,<sup>18,19</sup> and this could also affect anesthetic requirements.

The dose of thiopental for hypnosis was 17% less and that for anesthesia 18% less in pregnant women of 7–13 weeks' gestation compared with the dose needed by nonpregnant women. The anesthetic requirements at later stages of human pregnancy are unknown, but a reduction in isoflurane requirement has also been demonstrated in the postpartum period.<sup>20,21</sup>

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