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Pharmacokinetics and Plasma Binding of Thiopental. II: Studies at Cesarean Section

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This study was undertaken to investigate the effect of pregnancy on the disposition of thiopental and to determine the major factors which influence the placental transfer of the drug to the fetus. Maternal venous (M_V) and umbilical venous (U_V) and arterial (U_A) blood samples were collected at delivery from 11 pregnant women at term who received thiopental for induction of anesthesia for elective cesarian section. A detailed study of the pharmacokinetics of thiopental was carried out in 7 of these subjects and blood samples were collected for 80 to 100 hours following thiopental administration. A transient rise in thiopental plasma concentration was observed at delivery. Mean values of pharmacokinetic parameters (±SD) were: initial distribution volume (V_1) 17.3 l (±8.5), apparent volume of distribution ($V_{d\beta}$) 564 l (±343), volume of distribution at steady state (V_{ss}) 288 l (±180), systemic plasma clearance (Cl_p) 0.286 l/min (±0.156), rate of change of volume of distribution at zero time (RV_{d_0}) 1.03 l/min (±0.36) and elimination half-life ($t_{1/2}$) 26.1 h (±12.6). Comparison of these data with our previously reported data in nonpregnant surgical patients shows that $V_{d\beta}$, V_{ss}, and $T_{1/2}$ are significantly greater at cesarian section ($P < 0.05$) and that systemic plasma clearance shows a similar trend.

U_A and U_V values at delivery were similar within individuals. There was no correlation between the ratio U_V/M_V at delivery and the dosing-delivery interval (Δt), or between U_V and the administered dose or Δt. There were good correlations between U_V (corrected for dose) and the reciprocals of V_1, $V_{d\beta}$, V_{ss}, and plasma clearance of thiopental. This demonstrates that differences in maternal distribution and elimination characteristics of thiopental may be more important determinants of intersubject differences in fetal drug exposure than differences in dose or Δt. (Key words: Anesthesia: obstetrics. Anesthetics, intravenous: thiopental. Pharmacokinetics. Protein: binding.)

THIOPENTAL is extensively used in obstetrics for induction of anesthesia for cesarian section. The drug is eliminated in humans almost entirely by hepatic metabolism[1–3] and its hepatic extraction ratio is low in nonpregnant subjects.[4] Hence, its hepatic clearance and elimination half-life will be sensitive to the ability of the liver to metabolize the drug (hepatic intrinsic clearance) but insensitive to changes in liver blood flow.[5] An investigation of the pharmacokinetics of thiopental in pregnant women at cesarean section may yield information on the effect of pregnancy on the hepatic elimination of low-clearance drugs. Studies with several low-clearance anticonvulsant drugs in pregnant subjects led Eadie[6] to suggest that circulating progesterone may cause induction of hepatic drug-metabolizing enzymes in pregnancy.

Factors influencing the transfer across the placenta of thiopental administered to mothers near term have important consequences for the well-being of the fetus and neonate.[7] Past investigations of the placental transfer of thiopental have not fully clarified the relationships among the management of the mother, thiopental pharmacokinetics in the mother, blood concentrations of thiopental in the fetus at birth and neonatal physical status.[8,9] A wide intersubject variation in fetal umbilical blood concentration of thiopental at delivery has been observed which cannot adequately be accounted for by differences in maternal dose of thiopental or in thiopental dosage delivery interval.[8–11] This intersubject variation may be due to a variety of factors, including differences in the pharmacokinetics of thiopental among mothers due to, for example, pregnancy itself or the circulatory effects of vena-caval compression.[12,13]

The aims of our investigations were: 1) to determine the effect of pregnancy on the pharmacokinetics and plasma protein binding of thiopental, using data from our previous publication on thiopental pharmacokinetics in nonpregnant patients undergoing gynecologic surgery for comparison; and 2) to investigate the relationship between maternal pharmacokinetics of thiopental and the placental transfer of the drug.

Materials and Methods

The placental transfer of thiopental was investigated at delivery in 11 healthy pregnant women who gave birth to healthy infants (patient 13 gave birth to triplets) by elective cesarean section. In-

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formed consent was given by all patients and the project was approved by the Research Committee of the hospital. The patients received thiopental sodium by bolus (30 s) intravenous injection for induction of anesthesia. Patients were premedicated with scopolamine, and succinylcholine was administered to facilitate tracheal intubation. General anesthesia was maintained with nitrous oxide. The patients were placed on their backs and laterally tilted 10–15 degrees to the left with their arms extended to either side prior to anesthetic induction in an attempt to minimize supine hypotension resulting from caval compression by the gravid uterus. They remained in this position for the duration of anesthesia. The patients involved in the studies also received routine drug therapy as required clinically (*e.g.*, morphine for postoperative analgesia). A detailed investigation of the disposition of thiopental was carried out in 7 of these pregnant subjects (age 20–39 years, mean 30.1 years; weight 53–100 kg, mean 75.1 kg).

The plasma protein binding of thiopental was determined for 10 of the patients in plasma samples collected during the hour following thiopental administration.

The clinical protocol followed was similar to that described previously[4] and involved regular serial blood sample collection for a 3- to 4-day period following intravenous bolus administration of thiopental. More frequent (every few minutes) blood sampling was carried out prior to delivery. At delivery, maternal and fetal umbilical venous and, where possible, fetal umbilical arterial blood samples were obtained.

Thiopental was assayed in plasma by reverse-phase, high-performance liquid chromatography as described previously[4] and plasma protein binding of thiopental was determined by ultrafiltration.[14] Model-independent pharmacokinetic parameters of thiopental were obtained by fitting the plasma concentration-time data of each patient to the appropriate poly-exponential equation by nonlinear least squares regression as described previously.[4] The Mann-Whitney U test was used to evaluate differences between the subject groups. Correlations between variables were investigated by linear regression analysis. A probability value less than 0.05 was considered statistically significant.

Results

Plasma Protein Binding

The mean (±SD) percentage of thiopental bound to plasma proteins in samples collected during the first hour following thiopental administration was

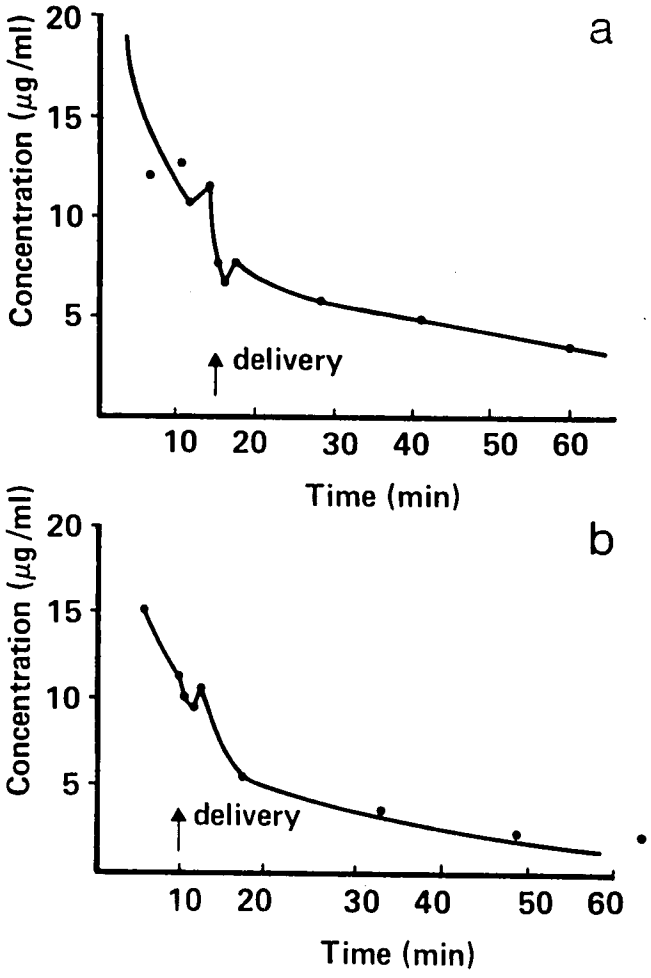

FIG. 1. Typical plasma concentration-time profiles of thiopental in the 1-h period following drug administration in Patient 9 (*a*) and Patient 12 (*b*). The times of delivery are indicated by the vertical arrows.

79.8 ± 5.0 per cent for 9 of the patients (concentration range 2–20 μg/ml). Percentage bound in the remaining subject (Patient 13) was 58.1 at a concentration of 1.1 μg/ml. Apart from this subject who gave birth to triplets, binding was similar to that previously reported by us[4] in healthy volunteers.

Disposition Kinetics

The data from 2 of the cesarean patients were best fitted by a bi-exponential equation while a tri-exponential equation was appropriate for the other 5 members of this group. The thiopental plasma concentration-time curves of all cesarean patients showed small secondary peaks at around the time of delivery, spanning on average a duration of about 5 min and this is illustrated in figure 1. Computer fitting of the plasma concentration-time data both with and without anomalous data had negligible effect on the

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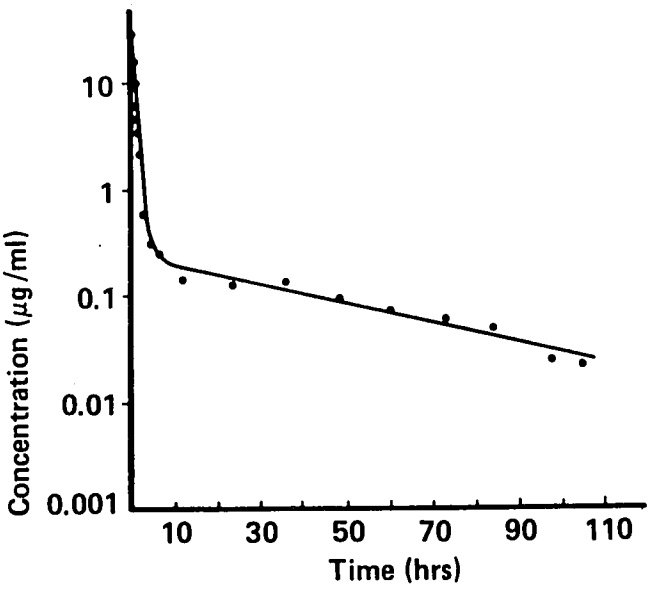

FIG. 2. Plasma concentrations of thiopental in Patient 12 following bolus intravenous administration of 450 mg. The curve was fitted by least-squares regression.

values of the pharmacokinetic parameters. An example of the computer fit is shown in figure 2. The pharmacokinetic parameters calculated for these patients are shown in table 1. There were significant correlations between body weight and $V_{d\beta}$ ($r = 0.84$, $P < 0.01$), and body weight and V_{ss} ($r = 0.73$, $P < 0.05$).

PLACENTAL TRANSFER

The time between thiopental dosing and delivery (Δt) and the concentration of thiopental in maternal peripheral venous (M_V), umbilical venous (U_V) and umbilical arterial plasma (U_A) at delivery for the 11 pregnant subjects at cesarian section are summarized in table 2.

There was no correlation between the Apgar score at 1 min or the time to regular respiration and either the umbilical arterial or umbilical venous plasma concentrations of thiopental at delivery. There was also no correlation between the ratio of umbilical venous/maternal venous plasma thiopental concentration at delivery and the dosing-delivery interval, between the maternal or umbilical venous plasma concentration of thiopental (normalized for dose by dividing by the administered dose in each case) at delivery and the reciprocal of the dose-delivery interval, or betwen the maternal or umbilical venous plasma concentration of thiopental at delivery and the administered dose.

There was a significant correlation between umbilical venous and arterial plasma concentrations of thiopental at delivery ($r = 0.98$, $P < 0.001$), between maternal and umbilical venous plasma concentrations of thiopental at delivery ($r = 0.88$, $P < 0.001$), and between maternal venous and umbilical arterial plasma concentrations of thiopental at delivery ($r = 0.89$, $P < 0.01$).

In the 7 patients in whom a detailed pharmacokinetic analysis was performed, both the maternal and umbilical venous plasma concentrations of thiopental at delivery (normalized for dose) were correlated significantly with $1/Cl_p$, $1/V_1$, $1/V_{d\beta}$, $1/V_{ss}$, and $1/RV_{d_0}$ (table 3).

Discussion

The plasma protein binding of thiopental in the pregnant patients, measured in plasma collected in the hour following thiopental administration, was similar to that determined previously in healthy volunteer subjects. Thiopental is bound predominantly to albumin in the plasma[15] and during the third trimester of pregnancy, the serum albumin concentration is reduced to approximately 75 per cent of normal.[16] It appears that thiopental binding is not affected by the moderate fall in serum albumin associated with pregnancy.

Following intravenous administration of thiopental for induction of anesthesia for elective cesarean section in 7 healthy pregnant women at term, a small

TABLE 1. Pharmacokinetic Parameters of Thiopental Following Intravenous Administration to Pregnant Patients Undergoing Elective Cesarian Section

	Body Weight (kg)	$t_{1/2\beta}$ (h)	V_1 (l)	$V_{d\beta}$ (l)	V_{ss} (l)	RV_{d_0} (l/min)	Cl_p (l/min)
Patient 6	60	22.2	4.97	105	60.2	0.464	0.055
Patient 7	92	38.2	11.4	822	265	0.965	0.251
Patient 8	75	6.0	22.2	287	191	1.34	0.559
Patient 9	74	15.1	31.7	433	259	0.640	0.335
Patient 10	53	23.2	24.3	371	245	1.24	0.185
Patient 11	72	45.7	12.2	752	304	1.02	0.192
Patient 12	100	32.3	14.3	1181	690	1.54	0.427
Mean ± SD	75 ± 15	26.1 ± 12.6	17.3 ± 8.5	564 ± 343	288 ± 180	1.03 ± 0.36	0.286 ± 0.156

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TABLE 2. Data on the Placental Transfer of Thiopental after Bolus Intravenous Injection Prior to Elective Cesarean Section

	Dose (mg)	Interval between Dosing & Delivery (min)	Plasma Concentration (μg/ml)			U_V/M_V	U_A/U_V	Apgar	Time to Regular Respiration (min)
			Maternal Venous M_V	Umbilical Venous U_V	Umbilical Arterial U_A				
Patient 6	350	22.0	26.0	20.3	22.0	0.78	1.10	8/10	<1.0
Patient 7	300	20.0	4.4	5.1	—	1.15	—	7/9	0.5
Patient 8	325	11.0	8.4	7.0	6.0	0.83	0.86	8/10	0.0
Patient 9	450	15.0	8.1	12.0	—	1.48	—	4/8	3.0
Patient 10	350	12.0	6.5	2.9	—	0.45	—	9/10	<1.0
Patient 11	450	7.0	19.4	16.7	14.1	0.86	0.84	9/10	<1.0
Patient 12	450	9.5	9.9	11.0	10.1	1.11	0.92	8/10	1.0
Patient 13(a)	400	7.8	22.0	33.9	30.5	1.54	0.90	6/9	2.0
Patient 13(b)	400	8.2	21.8	23.7	22.5	1.09	0.95	5/8	2.0
Patient 13(c)	400	9.0	19.6	26.3	22.8	1.34	0.87	4/9	2.0
Patient 14	500	21.0	6.5	8.0	—	1.23	—	9/10	0.5
Patient 15	400	11.0	6.9	5.4	3.6	0.78	0.67	9/10	1.0
Patient 16	400	9.5	19.5	27.8	21.3	1.43	0.77	7/10	2.0
Mean	—	—	—	—	—	1.08	0.87	—	—

secondary peak was observed in the thiopental plasma concentration-time curves of all subjects at around the time of delivery. This phenomenon was not observed in our previous study of nonpregnant women undergoing gynecologic surgery,[4] although the frequency of blood sampling in the pregnant group was much higher around the time of delivery than during surgery in the nonpregnant group. The manipulations involved in removing the fetus from the uterus, with the accompanying fluctuations in the pressure exerted on maternal blood vessels and disruption to normal blood flow in the area, may have given rise to the secondary peaks observed. Moore and McBride[17] observed secondary peaks in the plasma concentration time curve of diazepam administered to pregnant women during labour. However, the rise in diazepam concentrations occurred during the 18-hour period after parturition and was of a greater magnitude than that observed by us with thiopental. Moore and McBride[17] concluded that the phenomenon with diazepam was probably due to changes in physiology related to posture and exercise as their patients first became ambulant after delivery.

TABLE 3. Correlations Between Maternal and Umbilical Venous Thiopental Concentrations at Delivery Normalized for Dose and Pharmacokinetic Parameters (n = 7)

Parameter	M_V/Dose		U_V/Dose	
	r	P	r	P
$1/V_1$	0.88	<0.005	0.84	<0.01
$1/V_{d\beta}$	0.84	<0.01	0.73	<0.05
$1/V_{ss}$	0.87	<0.01	0.78	<0.025
$1/RV_{d_0}$	0.71	<0.05	0.78	<0.025
$1/Cl_p$	0.90	<0.005	0.80	<0.025

One of the aims of this study was to investigate the effects of pregnancy on the pharmacokinetics of thiopental. Table 4 provides a comparison of the data obtained in pregnant patients in this investigation with our previously reported data obtained in nonpregnant patients undergoing gynecologic surgery.[4]

The greatest difference observed between the pharmacokinetic parameters of the pregnant and nonpregnant groups was in the elimination half-life ($T_{1/2\beta}$). The mean half-life obtained in the nonpregnant group was 11.5 hours compared with 26.1 hours in the pregnant group. The range of values observed in the pregnant group (6.0–45.7 hours) was much wider than that observed in the nonpregnant group (9.7–12.7 hours). The longer elimination half-life in the pregnant group is due to a larger volume of distribution of the drug rather than a lower clearance. In fact, the clearance of thiopental was greater in the pregnant group. The elimination half-lives of several other low clearance, extensively metabolized drugs administered to pregnant women either during labor or prior to cesarian section have been reported. No change in half-life was observed with clorazepate[18]

TABLE 4. Comparison of the Pharmacokinetics of Thiopental Between Pregnant Women at Cesarean Section and Nonpregnant Patients Undergoing Gynecologic Surgery (Mean ± SD)

Parameter	Nonpregnant	Pregnant	P
Age (yr)	40.6 ± 15.7	30.1 ± 7.1	N.S.*
Weight (kg)	59.8 ± 8.4	75.1 ± 15.3	<0.1
V_1 (l)	13.8 ± 9.4	17.1 ± 8.5	N.S.
RV_{d_0} (l/min)	0.73 ± 0.36	1.03 ± 0.36	N.S.
$V_{d\beta}$ (l)	233 ± 98	564 ± 343	<0.05
V_{ss} (l)	97.5 ± 40	288 ± 180	<0.05
Cl_P (l/min)	0.150 ± 0.063	0.286 ± 0.156	<0.1
$t_{1/2\beta}$ (h)	11.5 ± 1.0	26.1 ± 12.6	<0.025

* Not significant.

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or amobarbital.[19] Longer half-lives were observed in pregnancy for nordiazepam[18] and diazepam[17] due in both instances to a larger volume of distribution. However, the elimination half-lives of both pancuronium[20] and oxazepam[21] were found to be shorter in pregnancy; in the case of pancuronium, this was due to a higher clearance of the drug. This interdrug variation in the effect of pregnancy on the elimination half-life appears to result (for the drugs cited above) from the variation in the net effect of two opposing tendencies: the tendency of the half-life to increase because of the higher volume of distribution in pregnancy, and the tendency of the half-life to decrease due to the higher drug clearance in pregnancy. In the case of clorazepate,[18] both volume of distribution and clearance were higher in pregnant subjects but elimination half-life was not significantly different from nonpregnant values.

The initial volume of distribution (V_1) and the initial rate of change of volume of distribution (RV_{d_0}) of thiopental were similar in both pregnant and nonpregnant subjects, although there was nearly a tenfold intersubject variation in the values of the initial volume of distribution. These results suggest that for a given dose, initial plasma concentrations and initial rate of drug distribution are similar in both groups of subjects. The higher apparent volume of distribution of thiopental in the pregnant subjects may be partly due to the changes in hemodynamics resulting from pregnancy[22] and the delivery and also to the higher body weight of the pregnant subjects. It should be pointed out though that apparent volume of distribution of thiopental only correlated with body weight within the pregnant group. This contrasts with the findings of our earlier study[4] where no correlation was found between any of the pharmacokinetic parameters and body weight and may be a result of the small sample sizes studied.

There was a trend to a higher total systemic plasma clearance in the pregnant subjects although the data, particularly of the pregnant group, were highly variable (range 0.055–0.559 l/min). Plasma clearance values were not corrected for body weight because there was no correlation between these two variables either within each group or in all twelve patients. The trend in pregnant subjects to a higher clearance of thiopental, a low clearance drug, is consistent with other reports[6,23–25] which suggest that in pregnancy, hepatic drug-metabolizing enzymes are in an induced state, particularly near term, and for several weeks postpartum.

It is not possible to determine to what extent the changes observed in the pharmacokinetic parameters of the pregnant subjects were due solely to pregnancy. As pointed out by Philipson,[26] data obtained from studies in pregnant women during cesarean section may not be representative for any stage of pregnancy except precisely cesarean section. In the present study, the data from the pregnant group were compared with data from nonpregnant women undergoing gynecologic surgery, in an attempt to take into account the effects of surgery on pharmacokinetics in the pregnant group. Another potential limitation on the data obtained from the pregnant patients at cesarean section is that delivery took place within about 20 min of thiopental administration, therefore for the majority of the study period the subjects were not pregnant. However, previous reports showing evidence in pregnancy of altered drug clearance[25] and of induction of hepatic microsomal enzymes,[23] demonstrated that the values for these parameters do not begin to return to nonpregnant levels until after the first week postpartum.

The lack of a correlation between the Apgar score at delivery and either the umbilical venous or arterial plasma concentrations of thiopental probably reflects the imprecision of this method of assessment of the effect of placentally transferred thiopental on neonatal physical status rather than the lack of an effect. The more precise neurobehavioral tests of Scanlon have demonstrated that maternally-administered thiopental has a broad-spectrum, nonspecific neurobehavioral depressant effect on the newborn.[7]

In the present study the mean U_V/M_V ratio obtained was approximately equal to one and there was no correlation found between the ratio U_V/M_V and either the dosing-delivery interval or the reciprocal of the dosing-delivery interval. The data indicate that transfer of thiopental across the placenta is rapid and this is consistent with findings from several earlier studies.[8,10,11,27] The mean value at delivery of the ratio U_A/U_V was 0.87 which indicates that, over the range of thiopental dosing-delivery intervals encountered (8–22 min), the drug distribution process throughout the fetus was nearing completion. This is consistent with the trend observed by Schepens and Heyndrickx[9] who reported a mean U_A/U_V ratio at delivery of 0.46 corresponding to thiopental dosing-delivery intervals in the range 4–7 min. These data suggest that equilibration of thiopental in the fetus is a relatively rapid process, and that in pharmacokinetic terms, for thiopental, the fetus may be viewed as a rapidly-equilibrating or shallow compartment.[28]

Several explanations have been proposed to explain the widely recognized phenomenon of an alert infant being born of a mother anesthetized with thiopental. These include the presence of an "adapt-

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ability response" of the infant to birth,[27] preferential uptake of thiopental by the fetal liver,[8,29] the higher relative water content of fetal brain,[27] the fall in P_{CO_2} at delivery,[27] and rapid redistribution of the drug into maternal tissues[9,11] causing a rapid reduction in the maternal-to-fetal concentration gradient. Any of the latter four factors might be expected to prevent thiopental from achieving sufficiently high concentrations in the fetal brain to cause depression. The results from the present study indicate that the rapid redistribution of thiopental in the maternal tissues occurring in the interval between dosing and delivery, is the major factor responsible for the discrepancy in the states of consciousness of the mother and neonate at delivery confirming results of earlier studies.[9,30] In the present study, venous plasma concentrations of thiopental in the umbilical cord, which would be similar to those entering the fetal brain, were well below arterial plasma concentrations of thiopental which have been reported necessary to produce anesthesia in adults (39–42 μg/ml).[31]

One of the major aims of this investigation was to identify the factors responsible for the large intersubject variation in the placental transfer of thiopental, as indicated by the umbilical venous concentration of the drug at delivery. Previous studies have demonstrated that the length of the thiopental dosing-delivery interval does not correlate with the umbilical blood concentration of thiopental at delivery[8] or with the condition of the newborn.[10,32] Furthermore, the protein binding of thiopental has been reported to be similar in maternal and fetal plasma,[8] therefore intersubject differences in umbilical blood concentrations of thiopental are presumably not due to differences between maternal and fetal plasma protein binding of thiopental. In the present study, the intersubject differences in the umbilical venous plasma concentrations of thiopental at delivery were not correlated with intersubject differences in the dose of thiopental administered nor with the dosing-delivery interval. However, at delivery, both maternal and umbilical venous plasma concentrations of thiopental normalized for dose correlated well with the reciprocal of volume of distribution and of systemic plasma clearance of thiopental. The plasma concentrations were normalized for the administered dose because linear pharmacokinetics apply for thiopental and therefore, plasma concentration of the drug at a given time is directly proportional to the administered dose. It appears, therefore, that intersubject differences of maternal distribution and elimination characteristics of thiopental may be more important determinants of intersubject differences of fetal drug exposure than differences of dose or of dosing-delivery interval. This is consistent with the fact that both volume of distribution and systemic plasma clearance of thiopental varied approximately tenfold among patients, whereas the dosing-delivery interval varied only about threefold and the dose administered less than twofold. The reason for the large intersubject variability in pharmacokinetic parameters of thiopental in the cesarean section patients may be related to the effect of caval compression by the gravid uterus during surgery. However, alterations in hemodynamics would not be expected to greatly affect the elimination of thiopental because hepatic clearance of this low clearance drug will be independent of changes in liver blood flow.[5] In our previous report,[4] in which the pharmacokinetics of thiopental were investigated in nonpregnant patients during gynecological surgery, there was only about a threefold variation of pharmacokinetic parameters observed among patients and therefore the large variability in the cesarean group is presumably not due to the surgery itself. An attempt was made to eliminate caval compression in the cesarian group by using a left lateral tilt, however, this may have been unsuccessful. Further studies of the placental transfer of thiopental need to be carried out in the absence of caval compression.

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