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Tissue Thiopental Concentrations in the Fetus and Newborn

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The distribution of thiopental was studied in tissues and organs of anencephalic human neonates and in fetal guinea pigs. The drug was administered by intermittent intravenous injections to the mother or by a single injection into the guinea pig fetus via the umbilical vein. High concentrations were found in the fetal liver, especially following direct injection into the fetus, in which case as much as 50 per cent of the dose could be accounted for in this organ. These findings document the importance of the fetal liver in preventing the fetal brain from being exposed to high concentrations of thiopental administered to the mother. (Key words: Thiopental; Tissue concentrations; Guinea pig fetus; Human neonate; Anencephaly.)

THIOPENTAL crosses the placenta rapidly[1-6] and appears in significant concentrations in umbilical-vein blood.[5,6] Yet the newborn infant is usually vigorous and cries spontaneously, in sharp contrast to the anesthetized state of the mother. This discrepancy has been attributed to the failure of thiopental, injected during labor and delivery, to reach the fetal brain in concentrations sufficient to cause depression.[5,6] Several mechanisms may be operating here.[6] Uterine contractions and compression of the umbilical cord both may impede entry of thiopental into the fetal circulation. Accumulation of thiopental in the liver either by vascular stasis or by binding to liver proteins, since a large part of the umbilical vein blood flows through this organ, may be another mechanism. A final factor could be the progressive dilution of the drug which occurs before it reaches the arterial side of the fetal circulation.

In order to confirm and quantify the role of the fetal liver, thiopental concentrations were determined in the plasma, liver, and other organs of anencephalic human newborns, guinea pig fetuses after administration of the barbiturate to the mother prior to delivery, and guinea pig fetuses which received thiopental directly by injection into the umbilical vein during their delivery by cesarean section.

Material and Methods

ANENCEPHALIC INFANTS

In two mothers fetal anencephaly had been diagnosed radiologically before labor. The nature of the fetal anomaly was explained to them and their consent for anesthesia and autopsy obtained. During labor, they received intravenous injections of thiopental sodium in 2.5 per cent concentration totaling 2,250 and 1,375 mg, respectively. These doses were administered over periods of 2.5 and 1.5 hours preceding delivery.

At delivery, blood samples were obtained from the antecubital vein or the brachial artery of the mother and from the umbilical vessels of a doubly clamped segment of the cord.

The two infants, weighing 2,200 g and 2,320 g, respectively, died 22 and 50 minutes after delivery; necropsy was done within 30 minutes of demise. Blood was obtained from

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TABLE 1. Thiopental Concentrations in Maternal Blood and in Blood and Tissues of Two Anencephalic Human Newborns Following Intravenous Administration to the Mothers*

	Thiopental Concentration	
	Infant A (μg/ml)	Infant B (μg/ml)
Blood samples		
Maternal	(vein) 19.0	(artery) 19.3
Umbilical vein	11.0	14.0
Umbilical artery	10.0	11.7
Newborn heart (postmortem)	5.9	9.7
	(μg/g)	(μg/g)
Newborn tissue samples		
Subcutaneous fat	88.0	43.3
Liver, left lobe	65.0	42.6
Liver, right lobe	58.0	38.0
Thyroid	—	16.6
Lung	25.0	13.7
Kidney	16.0	10.6
Pancreas	15.0	14.0
Spleen	15.0	11.1
Spinal cord	—	11.1
Myocardium	9.7	10.4
Thymus	—	9.9
Skeletal muscle	—	9.1

* The mother of Infant A received 2,250 mg of thiopental over a period of 2.5 hours; the mother of Infant B, 1,375 mg, over a 1.5-hour period.

the heart, and the following organs and tissues were sampled: liver (right and left lobes), spleen, pancreas, kidney, heart, lung, thyroid, thymus, spinal cord, skeletal muscle, and subcutaneous fat. All samples were analyzed for thiopental content using a spectrophotofluorometric method described previously.[7] This method is highly sensitive, allowing determination of thiopental concentrations as low as 0.1 μg/ml of plasma and 0.1 μg/g of tissue. Its accuracy has been estimated to be ±10 per cent. It is also highly specific, so that concurrent administration of secobarbital did not interfere with determinations of thiopental.

GUINEA PIGS: MATERNAL INJECTIONS

Each of two pregnant guinea pigs at term received intermittent injections of 0.5 ml thiopental sodium, 1.25 per cent, through a plastic catheter introduced into the external jugular vein. Total doses of 50 and 62.6 mg, respectively (approximately 50 mg/kg), were administered over periods of 44 and 55 minutes preceding delivery by cesarean section. Upon delivery, the fetuses were killed by stunning. Blood samples were immediately obtained from the heart. Organs and tissues removed for analysis included the following: liver, kidney, spleen, striated muscle, heart, lungs, spinal cord, and brain. Subcutaneous fat in the fetal guinea pig is too scanty for sampling. A maternal blood sample was also obtained at delivery.

GUINEA PIGS: FETAL INJECTION

In this set of experiments, fetuses from three pregnant guinea pigs anesthetized with secobarbital, 10 mg/kg iv, were delivered by cesarean section. Prior to delivery of each fetus, a loop of umbilical cord was exteriorized through a small incision in the uterine horn and a dose of 2.5 mg thiopental sodium (approximately 35 mg/kg) in 0.5 per cent concentration was injected into the umbilical vein over a period of about a minute. The cord was clamped at the end of the injection. Two minutes later the fetus was delivered and killed by stunning; a blood sample was obtained at once from the heart. Organ tissue samples from the fetal brain, spinal cord, and left and middle lobes of the liver were then obtained. A total of six fetuses was studied.

TABLE 2. Blood and Tissue Concentrations of Thiopental in Guinea Pigs after Maternal Administration (50 mg/kg iv), Mean Values of Two Mothers and Seven Fetuses

	Thiopental Concentration ± SD (μg/ml)
Maternal blood	15.4 ± 0.6
Fetal blood	10.0 ± 1.3
	(μg/g)
Fetal	
Liver*	64.7 ± 6.5
Skeletal muscle	32.4 ± 3.0
Myocardium	27.6 ± 4.1
Spinal cord	19.4 ± 2.7
Kidney	19.3 ± 1.9
Spleen	18.7 ± 2.8
Lung	16.7 ± 1.2
Brain	15.0 ± 2.3

* In one litter mean thiopental concentrations were: 70.6 ± 9.2 μg/g in the middle lobe; 68.3 ±8.9 μg/g in the left lobe.

TABLE 3. Tissue Concentrations of Thiopental in Six Guinea Pig Fetuses after Injection into the Umbilical Vein of Approximately 35 mg/kg*

	Fetus 1 (μg/ml)	Fetus 2 (μg/ml)	Fetus 3 (μg/ml)	Fetus 4 (μg/ml)	Fetus 5 (μg/ml)	Fetus 6 (μg/ml)
Blood	0.8	6.6	13.0	28.0	0.9	7.2
	(μg/g)	(μg/g)	(μg/g)	(μg/g)	(μg/g)	(μg/g)
Liver						
Middle lobe	230	765	990	950	288	979
Left lobe	22.2	376	140	220	28.8	492
Brain	2.9	5.0	11.0	25.0	3.1	5.4
Spinal cord	5.5	—	15.0	28.0	8.6	—

* Accuracy of the determination is estimated to be ±10 per cent.

Results

ANENCEPHALIC INFANTS

Thiopental concentrations in maternal blood were substantially higher than those in the umbilical artery and vein, which were very similar in the two infants (table 1). Thiopental levels in different organs and tissues of the two human newborns have been listed in order of decreasing concentrations. Although drug concentrations were higher in Infant A, reflecting the greater maternal dose, the relative tissue levels of the barbiturate were similar in the two infants. The subcutaneous fat contained the highest concentrations of thiopental (88.0 and 43.3 μg/g, respectively). The second highest concentrations were found in the liver, amounting in Infant A to 65.0 μg/g in the left lobe and 58.0 in the right lobe. The corresponding values in Infant B were 42.6 and 38.0 μg/g. In contrast to these tissues, the spinal cord of Infant B contained only 11.1 μg/g thiopental.

GUINEA PIGS: MATERNAL INJECTIONS

Table 2 shows thiopental levels in maternal and fetal blood and various fetal organs following intermittent administration of the drug to two pregnant guinea pigs. There was a substantial gradient in thiopental concentration (15.4 *vs.* 10.0 μg/ml) between maternal and fetal blood. Like the livers in the anencephalic human newborns, the fetal livers contained concentrations of thiopental two to four times greater than those found in the other fetal organs and tissues sampled. In one litter mean thiopental levels in the left and middle lobes of the fetal liver were determined separately. They were almost identical: 68.3 μg/g in the left lobe and 70.6 μg/g in the middle lobe. Again as in the anencephalic infants, drug levels in the spinal cord were relatively low (19.4 μg/g). Concentrations in the brain were even lower, amounting to 15.0 μg/g.

GUINEA PIGS: FETAL INJECTIONS

Fetal blood and tissue levels after a single injection into the umbilical vein are shown in table 3. Despite the large variations in thiopental concentrations among individual fetuses, the distributions of the barbiturate within all fetuses were very similar. The highest concentrations of the drug, 230 to 990 μg/g, were found in the middle lobe of the liver, compared with 22.9 to 492 μg/g in the left lobe. The weights of the middle lobes ranged from 0.9 to 1.6 g. Thus, in four of six fetuses this lobe contained approximately half of the injected dose of thiopental. As in the maternal-injection group, barbiturate levels in the spinal cord and in the brain were much lower (5.5 to 28.0 and 2.9 to 25.0 μg/g, respectively.

Discussion

These results demonstrate the role of the fetal liver in the distribution of thiopental which crosses the placenta. In the human newborn, only subcutaneous fat contained larger concentrations of the barbiturate (table 1). This is undoubtedly due to the high lipid solubility of thiopental and to the fact that the mothers received repeated injections of the drug over relatively long periods.

The major part of umbilical venous blood perfuses the fetal liver, and only a small frac-

tion is shunted directly into the inferior vena cava via the ductus venosus.[8] Thus, any drug crossing the placenta is immediately brought to the fetal liver. In most of our experiments, thiopental levels were determined separately in the left and right lobes of the liver in human newborns and in the left and middle lobes of the liver in guinea pig fetuses. This was deliberate, since in the human fetus the left lobe of the liver receives blood mostly from the umbilical vein, while the right lobe is supplied mostly by blood from the portal vein[9]; in the fetal guinea pig the middle and left lobes of the liver are perfused mainly by umbilical and portal veins, respectively. Following repeated maternal injections of thiopental in humans or guinea pigs, the two lobes of the fetal liver contained almost equal concentrations of the drug (tables 1 and 2). Prolonged exposure of the fetus to thiopental and its recirculation within the fetal body will produce nearly identical drug concentrations in all fetal vessels, as observed in the umbilical vessels of the two human anencephalic infants (table 1).

When a single dose of thiopental was injected into the fetus via the umbilical vein, the drug concentration in the middle lobe of the liver, perfused mainly by this vessel, was two to ten times greater than that in the left lobe (table 3). In most fetuses the total amount of thiopental in the middle lobe was nearly half the injected dose.

The high thiopental uptake by the liver could be due not only to the pattern of fetal circulation but also to the presence of two cytoplasmic protein fractions (Y and Z proteins) in the hepatic cells, which appear to be important in the uptake of organic anions from the plasma.[10] Substantial hepatic uptake of drugs transmitted to the fetus across the placenta has also been demonstrated with ^{82}Br-halothane,[11] lidocaine,[12] and ^{14}C-cyclamate.[13]

Thiopental levels in the brain and spinal cord were generally low following direct administration of the drug to guinea pig fetuses (table 3). This provides experimental support for the conclusions drawn from a clinical study in humans that, following a single maternal injection of thiopental, the fetal liver prevents the brain from being exposed to excessive concentrations of the drug. Placental uptake of thiopental does not appear to be important in this respect.[14]

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