

# The Kinetics of Transfer of Lidocaine (Xylocaine®) across the Human Placenta

Sol M. Shnider, M.D.,\* and E. Leong Way, Ph.D.†

Lidocaine, 2 or 3 mg./kg., was administered intravenously to 16 healthy women prior to vaginal delivery and to nine prior to elective cesarean section. Maternal arterial lidocaine concentrations rose rapidly and then declined, with a decay curve of two half-lives, one lasting 30 seconds and the other 30 minutes.

Umbilical venous and arterial samples were obtained at birth. Lidocaine appeared in cord blood within two minutes of maternal administration and remained in measurable quantities for 30–45 minutes. Mean umbilical venous lidocaine levels were only 55 per cent of simultaneous maternal arterial levels. From subsequent neonatal samples, the lidocaine decay half-lives were found to be similar in mother and infant.

Specimens of placental tissue from five patients who had not received lidocaine were homogenized and incubated with lidocaine; the homogenates did not metabolize lidocaine. Fetal and maternal plasma were separated by a semipermeable membrane, and lidocaine added to maternal plasma; after incubation, no fetal-maternal concentration gradient was found. Using an ultrafiltration technique it was found that the degrees of plasma-protein binding of lidocaine by maternal and fetal blood were similar.

The fetal-maternal lidocaine concentration gradient seen *in vivo* is discussed; possible explanations, including a placental diffusion barrier, are examined.

IT IS NOW ESTABLISHED that local anesthetics such as lidocaine, mepivacaine and prilocaine, when used to provide obstetrical anesthesia, are transferred across the human placenta to

the fetus.<sup>1-3</sup> However, there is little precise quantitative information available on the kinetics of transfer of these drugs. This paper reports the results of our studies with lidocaine: the rate of placental transfer, transplacental concentration gradients, placental metabolism of lidocaine, protein binding of the drug by maternal and fetal blood, and the fate of lidocaine in plasma of the newborn during the first hour after birth.

## Rate of Placental Transfer

### METHOD

Sixteen healthy full-term pregnant women, who had given informed consent, received single intravenous injections of 1 per cent lidocaine hydrochloride (Xylocaine®), 2 mg./kg., at a rate of 100 mg./min. The total dose varied between 100 and 150 mg. and was administered 30 seconds to 43 minutes before uncomplicated vaginal delivery. Prior to drug administration, a sample of blood was drawn for "blank" determination. No drug which might have interfered with analysis for lidocaine had been given previously. Immediately following delivery, samples of blood were drawn simultaneously from a maternal artery and from an umbilical vein and an artery in a doubly-clamped segment of umbilical cord. The latter were considered representative of fetal blood.

The concentrations of lidocaine in these samples were determined spectrophotometrically, using a modification of the methyl orange method of Sung and Truant.<sup>4</sup> Benzene was used as the extraction solvent; after coupling the drug with methyl orange, sensitivity was enhanced by extracting the dye complex in a small volume of dilute hydrochloric acid, for spectrophotometric estimation. A high degree of specificity for lidocaine was attained by

\* Associate Professor of Anesthesia and Associate Professor of Obstetrics and Gynecology.

† Professor of Pharmacology.

Received from the Departments of Anesthesia, Pharmacology, Obstetrics and Gynecology, University of California Medical Center, San Francisco, California 94122. Accepted for publication February 29, 1968. Supported in part by a grant-in-aid from Astra Pharmaceutical Company, Worcester, Massachusetts, and by National Institutes of Health Research Grant GM 01839.

washing the alkaline solvent extract of the drug with a 0.5 M phosphate buffer of pH 6.2 before forming the drug-dye complex with methyl orange. With this modified method, recoveries of lidocaine added to maternal or fetal plasma averaged 95 per cent, and the optical density was linearly related to concentration between 0.2 and 15.0  $\mu\text{g./ml.}$  Values for plasma blanks in both venous and arterial blood of 15 mothers prior to administration of lidocaine and in umbilical venous and arterial blood at birth in 11 infants whose mothers had received no lidocaine were determined. There was no significant difference in values of blanks among the various blood samples. Plasma lidocaine levels were corrected for individual blanks which were equivalent to less than 0.4  $\mu\text{g./ml.}$  of lidocaine.

### RESULTS

Lidocaine appeared in umbilical venous blood within two to three minutes. After six minutes, the ratios between maternal arterial and umbilical venous blood remained fairly constant (fig. 1). The anesthetic was also found in umbilical arterial blood approximately six minutes following administration. After

this time, blood levels in mother and fetus declined, and by 30 to 45 minutes the lidocaine concentration approached the lower limits of sensitivity of the method. In no case did the lidocaine concentration in fetal blood exceed that in maternal blood.

### Transplacental Concentration Gradients

#### METHOD

In nine healthy mothers undergoing elective repeat cesarean section with light general anesthesia (thiopental-nitrous oxide-succinylcholine) lidocaine, 3 mg./kg., was administered intravenously at a rate of 100 mg./minute. Total dosage varied between 183 and 504 mg. Maternal blood pressure and pulse were measured at one-minute intervals for 15 minutes following administration of lidocaine, then every five minutes for the duration of surgery. An indwelling arterial needle was placed in the maternal brachial artery and a sample was taken for a blank determination before drug administration. Following administration of lidocaine, arterial samples were taken at  $\frac{1}{4}$ ,  $\frac{1}{2}$ , 1, 2, 4, 8, 16, 32, 64 and 128 minutes. In addition, just before delivery of five infants,

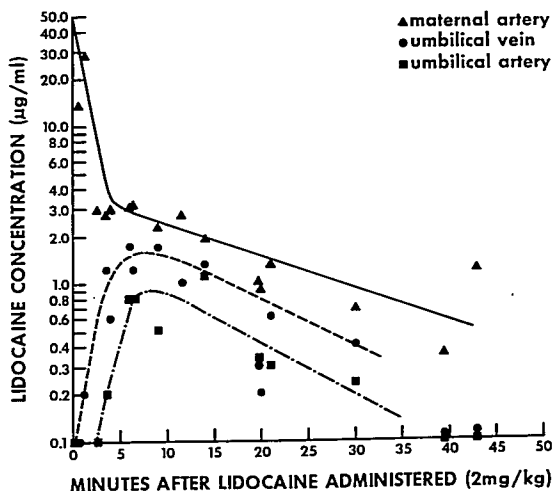


FIG. 1. Plasma concentration of lidocaine at birth, in maternal artery (▲), umbilical vein (●) and umbilical artery (■) following single intravenous injection of the drug (2 mg./kg.) in 16 mothers.

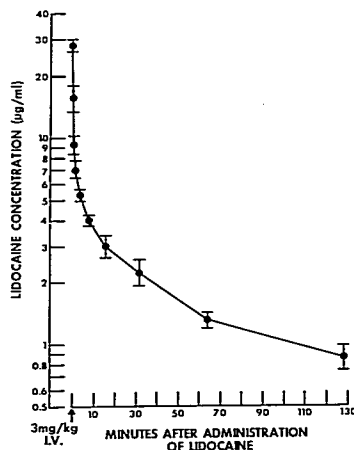


FIG. 2. Mean concentration of lidocaine ( $\pm$  S.E.) in maternal arterial plasma following single intravenous injection of the drug (3 mg./kg.) to mothers during light general anesthesia for cesarean section.

blood was drawn simultaneously from the maternal artery and the uterine vein. At the time of delivery of all infants, simultaneous samples were taken from the maternal artery,

umbilical vein, and umbilical artery, and analyzed for lidocaine concentration.

### RESULTS

From the mean lidocaine decay curve in the maternal artery (fig. 2) it is apparent that the rate of change of lidocaine concentration has at least two components, with half-lives of approximately 30 seconds and 30 minutes, respectively. In the first few minutes, arterial plasma levels of the drug declined rapidly: at  $\frac{1}{4}$  minute, the mean level was 28  $\mu\text{g./ml.}$ , while at five minutes it was 5  $\mu\text{g./ml.}$  Thereafter, the lidocaine concentration fell more slowly, and by 16 minutes it was 3  $\mu\text{g./ml.}$ ; by 35 minutes, 2  $\mu\text{g./ml.}$ ; by 100 minutes, 1  $\mu\text{g./ml.}$  There were no apparent toxic manifestations. Maternal blood pressure and pulse rate were not altered beyond  $\pm 10$  per cent following administration of lidocaine.

Delivery of the infant occurred between seven and 39 minutes after administration of lidocaine (table 1). The mean maternal artery lidocaine concentration at birth was  $2.8 \pm 1.1$  (S.D.)  $\mu\text{g./ml.}$  This concentration was significantly higher ( $P < 0.01$ , Student's  $t$  test) than in either of the umbilical vessels: mean umbilical vein  $1.6 \pm 0.94$   $\mu\text{g./ml.}$ , and mean umbilical artery  $1.2 \pm 0.85$   $\mu\text{g./ml.}$  The mean ratio of drug concentration between the maternal blood going to the uterus (maternal artery) and leaving it in fetal blood

TABLE 1. Data of Nine Patients Who Received Intravenous Lidocaine (3 mg./kg.) during General Anesthesia for Cesarean Section

Patient	Interval between Lidocaine Administration and Birth (Cord Clamping). (min.)	Total Lidocaine Dose (mg.)	Lidocaine Concentration in Plasma $\mu\text{g./ml.}$			Ratio (per cent)*		
			Maternal Artery	Umbilical Vein	Umbilical Artery	UV/MA	EA/MA	UA/UV
1	7	230	4.9	2.9	2.5	59	51	86
2	12-1/2	222	3.5	3.4	2.8	97	80	82
3	15	225	2.4	1.7	0.8	71	33	47
4	16	195	1.7	0.8	0.7	47	41	88
5	19	183	2.2	1.3	0.9	59	41	69
6	21	282	3.8	1.0	0.7	26	18	70
7	21	341	2.4	0.3	0.8	54	33	61
8	32	220	1.7	0.7	0.5	41	29	71
9	39	504	2.9	1.1	0.9	38	31	82
Mean			2.8	1.6	1.2	55	40	73
S.D.			$\pm 1.1$	$\pm 0.94$	$\pm 0.85$			

\* UV = umbilical vein; MA = maternal brachial artery.

(umbilical vein) was 55 per cent, and this gradient was still considerable 39 minutes after drug administration. The concentration gradient between the uterine vein and the umbilical vein is illustrated in figure 3 (which shows schematically the uterine and placental blood flow on maternal and fetal sides of the placenta). It is apparent again that even after 39 minutes a significant gradient for lidocaine exists between the blood leaving the placenta and that entering the fetus.

### Placental Metabolism of Lidocaine

#### METHOD

Five separate placental homogenates were prepared from tissues obtained immediately after delivery.<sup>7</sup> Placentas from mothers who had received lidocaine and those with known systemic disease were avoided. The placenta was delivered directly into refrigerated sterile isotonic saline solution in order to preserve enzymes. With two pairs of forceps, the placental villi were teased apart, separated and placed in Petri dishes of cold saline solution. Tissue was removed from all portions of the placenta except necrotic or traumatized areas, blood vessels and infarcts. The tissue was washed thoroughly in several cold saline baths until blood-stained fluid was no longer visible. The tissue was blotted with filter paper and weighed. Nine gm. of tissue was placed in a cold porcelain mortar with a dou-

ble volume of 0.2 M phosphate buffer at pH 7.4 and homogenized by hand. Lidocaine was added to make a substrate concentration of 5  $\mu$ g./ml. The mixture was immediately incubated aerobically under constant agitation for 120 minutes at 37° C. and pH 7.4. Samples of two ml. were removed every half hour and analyzed for lidocaine. For comparison, the same procedure was performed with fresh adult rabbit liver homogenate, as described by Hullunger.<sup>8</sup>

#### RESULTS

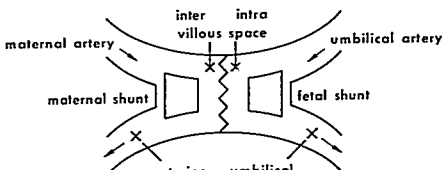
Under conditions that resulted in rapid biotransformation of lidocaine by rabbit liver, human placenta exhibited little or no activity. After 60 minutes of incubation, a mean of 98 per cent of the original lidocaine was recovered from the placental homogenate, while only 22 per cent was recovered from the liver (fig. 4).

### Protein Binding of Lidocaine in Maternal and Fetal Blood: Dialysis

#### METHOD

Three experiments were performed with maternal and their respective fetal bloods obtained from healthy unmedicated obstetrical patients undergoing vaginal delivery. Lidocaine was added to plasma from the fetus to reach a concentration of 5  $\mu$ g./ml. Aliquots of 5 ml. were placed in cellophane dialysis bags,

FIG. 3. Placental gradient for lidocaine between maternal uterine vein and fetal umbilical vein. In five patients who received the drug intravenously (3 mg./kg.) during light general anesthesia for cesarean section, the mean fetal/maternal ratio was 45 per cent.



Patient Number	Interval between I.V. Lidocaine 3mg/kg and Birth	Lidocaine $\mu$ g/ml		Umbilical Vein / Uterine Vein $\times 100$
		uterine vein	umbilical vein	
3	15 min	2.5	1.7	68 %
6	21	3.2	1.0	31.4
7	21	2.5	1.3	52
8	32	1.6	0.7	43.7
9	39	3.7	1.1	29.6
Mean		2.7	1.2	45 %

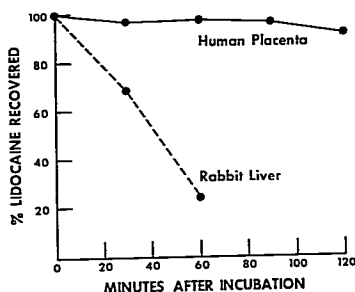


FIG. 4. Rates of metabolism of lidocaine by the human placenta (solid line—mean of three experiments) and rabbit liver (broken line—one experiment).

which were tightly tied and placed in glass tubes containing either 5 ml. of maternal plasma or 5 ml. of saline solution. The tubes were stoppered and attached to a rotating wheel in an air incubator at 37° C. and dialyzed for 24 hours.

#### RESULTS

Lidocaine was found in equal concentrations (2.5  $\mu\text{g./ml.}$ ) in fetal plasma, maternal plasma and saline.

#### Protein Binding of Lidocaine in Solution of Maternal and Fetal Blood: Ultrafiltration

The effects of increasing plasma concentration of lidocaine on protein binding in maternal and fetal blood were compared using the method of Laviates.<sup>9</sup>

#### METHOD

Lidocaine was added to paired 5 ml. aliquots of maternal and fetal plasma to achieve equal concentrations of 2, 5, 8 and 12  $\mu\text{g./ml.}$  The plasma was introduced into a glass chamber containing mercury and separated from an identical receiving chamber by a cellophane membrane. Pressure was applied to the plasma by a column of mercury raised to a height of 39 cm. above the mercury in the receiving chamber, and after 24 hours the ultra-filtrate was removed from the receiving chamber. Lidocaine was analyzed in both protein-free filtrate and plasma residue. The

lidocaine bound to plasma protein was easily removed by alkaline solvent extraction; hence, no difficulty was encountered in the estimation of the compound by the methyl orange procedure.

#### RESULTS

Protein binding of lidocaine by fetal blood was essentially the same as that of maternal blood (fig. 5). The degree of protein binding varied with the concentration of lidocaine in plasma. At low concentrations (2  $\mu\text{g./ml.}$ ) practically all the lidocaine was bound to protein, whereas at high concentrations (12  $\mu\text{g./ml.}$ ) approximately 30 per cent was bound.

#### Lidocaine Blood Levels in Mother and Newborn After Birth

#### METHOD

From six mothers who had received lidocaine, 3 mg./kg., intravenously during elective cesarean section, samples were drawn from the maternal artery and umbilical artery at birth. Approximately one hour later, samples were taken from the femoral vein of the vigorous newborn and from the maternal artery.

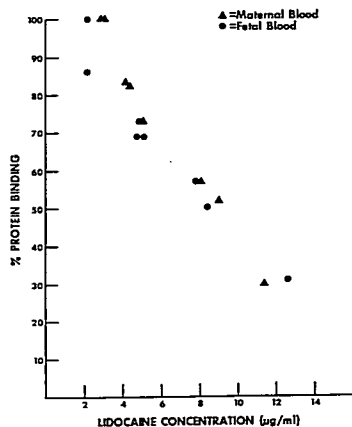


FIG. 5. Experiment on lidocaine ultrafiltration. Note relative decrease in plasma protein-binding of lidocaine with increasing plasma lidocaine concentrations in both maternal blood ( $\Delta$ ) and fetal blood ( $\bullet$ ).

Each sample was analyzed for lidocaine concentration.

### RESULTS

In the hour or so following birth, the slopes of the lidocaine decay curves were roughly the same in maternal and newborn blood (fig. 6), suggesting that the newborn distributed and/or metabolized and/or excreted lidocaine at approximately the same rate as the mother. However, it should be noted that the lidocaine levels in the newborn were at the lower limits of precision of the procedure.

### Discussion

The earliest investigation of placental transfer of local anesthetics was done by Bromage in 1961.<sup>4</sup> He found that if large doses of lidocaine were given to mothers for epidural anesthesia, measurable quantities crossed the placenta into the fetal circulation. Since then, similar findings of placental transfer for mepivacaine<sup>4</sup> and prilocaine<sup>5, 6</sup> have been reported.

Since the placental transfer of basic drugs by passive diffusion would be governed largely by the lipid solubility of the nonionized molecule,<sup>10</sup> it is not surprising that a base such as lidocaine ( $pK_a = 7.86$ ; oil-water distribution ratio at  $pH\ 7.20 = 30.2$ )<sup>11</sup> should cross the placenta easily and rapidly. Our measurements indicate that lidocaine was transmitted across the placenta within two to three minutes after appearing in the maternal circulation. However, a large maternal-fetal lidocaine concentration gradient still persisted for as long as 40 minutes after administration of the drug (fig. 1).

Theoretically, the transplacental gradient for lidocaine should be observed best in the placenta between the fetal intravillous and the maternal intervillous space (fig. 3), rather than in the maternal artery or uterine vein and the umbilical vein. Intravillous fetal capillary blood, however, is not easily sampled. Maternal intervillous blood can be aspirated easily.<sup>12</sup> However, contents of oxygen, carbon dioxide and, presumably, lidocaine, may vary depending on the proximity of the needle to any of the many arterioles which supply the space. It might be expected that uterine venous blood would be a good reflection of the "mixed" maternal blood bathing the fetal

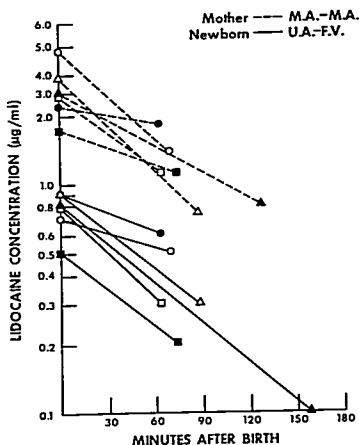


FIG. 6. Plasma lidocaine concentration in maternal artery (M.A., broken line) and umbilical artery at birth and in newborn femoral vein one to two hours after birth (U.A.-F.V., unbroken line). Lidocaine, 3 mg/kg., was administered to the mothers during general anesthesia for cesarean section, 12 to 32 minutes before delivery and initial sample.

villi; however, this is debatable since uterine venous blood also is derived from uterine muscle which has no contact with the fetus. Similarly, on the fetal side, although it would appear that umbilical venous blood is that blood which comes into equilibrium with maternal blood in the placenta, one cannot rule out functional or anatomical shunts between umbilical arterioles and venules.<sup>13</sup> Nevertheless, it appears that a reasonable indication of the transplacental concentration gradient for lidocaine can be obtained by examining, simultaneously, blood from the maternal artery or uterine vein and the umbilical vein. Our studies on patients undergoing cesarean section also indicated a substantial transplacental concentration gradient of lidocaine, irrespective of the interval since administration of lidocaine and the amount of lidocaine administered.

We attempted to find an explanation for this gradient. One possibility was placental metabolism of lidocaine. The placenta is rich in

enzymes; at least 60 have been found in the normal placenta.<sup>14</sup> If this organ contains enzyme systems similar to those in liver microsomes,<sup>8</sup> capable of oxidatively metabolizing lidocaine before it reaches the fetal side of the placenta, the lower concentration of lidocaine in the fetus could thus be explained. However, we found no evidence for placental metabolism of the drug. Another possible explanation for the gradient might be a difference in the capacities for protein-binding or plasma-carrying of lidocaine by maternal and fetal blood. For instance, a greater affinity of maternal protein for lidocaine would result in a higher lidocaine concentration in the maternal plasma. We found no evidence for such a difference.

A plausible explanation for the existence of a concentration gradient for lidocaine between mother and fetus would be a placental "barrier." Although lidocaine penetrates the placental membrane rapidly, a factor apparently exists which limits and governs its rate of transfer. This factor would be dependent in part on the physicochemical properties of the drug, but hemodynamic factors, such as uneven distribution of maternal perfusion and fetal circulation through the placenta and the possibility of arteriovenous shunts in the fetal placenta, cannot be excluded by the present study.

### Summary

Following intravenous administration of lidocaine to the mother, the local anesthetic was detected in fetal blood within two to three minutes. Irrespective of amount of lidocaine administered, or the time interval between drug administration and blood sampling, there was usually a large transplacental concentration gradient. The mean ratio of umbilical venous to maternal arterial blood, after intravenous administration of 3 mg./kg., was 55 per cent (range 38 to 97 per cent). This gradient could not be explained by placental metabolism of lidocaine or by a difference in protein-binding characteristics of maternal and fetal blood. Since the maternal and newborn plasma decay curves for lidocaine were roughly similar, it is postulated that the lidocaine transplacental concentration gradient may be the result of a "barrier"

which limits the rate of diffusion of lidocaine. However, hemodynamic factors and the possibility of arteriovenous shunts in the fetal placenta are alternative explanations that have not been completely excluded.

The authors are grateful to Mrs. Marilyn J. Lord for valuable technical assistance, and to Drs. William K. Hamilton, Grant Wilkinson, and E. I. Eger for constructive criticism.

### References

1. Bromage, P. R.: Continuous lumbar epidural analgesia for obstetrics, *Canad. Med. Assoc. J.* 85: 1136, 1961.
2. Beckett, A. H., Boyes, R. N., and Parker, J. B. R.: Determination of lignocaine in blood and urine in human subjects undergoing local anesthetic procedures, *Anaesthesia* 20: 294, 1965.
3. Epstein, B. S., and Coakley, C. S.: Passage of lidocaine and prilcaine across the placenta, *ANESTHESIOLOGY* (Work in progress abstract) 26: 246, 1967.
4. Morishima, H. O., Daniel, S. S., Finster, M., Poppers, P. J., and James, L. S.: Transmission of mepivacaine hydrochloride (Carbocaine) across the human placenta, *ANESTHESIOLOGY* 27: 147, 1966.
5. Poppers, P. J.: Practical and theoretical consideration on the use of prilcaine in obstetrics, *Acta Anaesth. Scand. Suppl.* 25: 385, 1968.
6. Sung, F., and Truant, A. P.: The physiological disposition of lidocaine and its comparison in some respects with procaine, *J. Pharmacol. Exp. Ther.* 112: 432, 1954.
7. Moya, F., and Margolies, A. B.: Hydrolysis of succinylcholine by placental homogenates, *ANESTHESIOLOGY* 22: 11, 1961.
8. Hullunger, G.: On the metabolism of lidocaine, *Acta Pharmacol. Toxicol.* 17: 365, 1960.
9. Lavietes, P. H.: Anaerobic ultrafiltration, *J. Biol. Chem.* 120: 267, 1937.
10. Moya, F., and Thordike, V.: Passage of drugs across the placenta, *Amer. J. Obstet. Gynec.* 84: 1778, 1962.
11. Bromage, P. R.: A comparison of the hydrochloride salts of lignocaine and prilcaine for epidural analgesia, *Brit. J. Anaesth.* 37: 753, 1965.
12. Sjostedt, S., Rooth, G., and Caligara, F.: The oxygen tension of the blood in the umbilical cord and intervillous space, *Arch. Dis. Child.* 35: 529, 1960.
13. Stembera, Z. K., and Hodr, J.: Disturbances in the placental circulation in threatened foetal asphyxia (in Czech), *Cs. Gynek.* 28: 654, 1963.
14. Eastman, N. J., and Hellman, L. M.: *Williams Obstetrics*. New York, Appleton-Century Crofts, Inc., p. 148, 1961.