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Pharmacokinetics of Lidocaine in Fetal and Neonatal Lambs and Adult Sheep

Hisayo O. Morishima, M.D., Ph.D., Mieczyslaw Finster, M.D.,† Hilda Pedersen, M.D.,‡ Atsuo Fukunaga, M.D.,§ Robert A. Ronfeld, Ph.D.,¶ Helen G. Vassallo, Ph.D.,** Benjamin G. Covino, Ph.D., M.D.††*

The pharmacokinetics of lidocaine were studied in fetal and neonatal lambs and in pregnant and nonpregnant adult sheep. Catheters were implanted in the femoral vessels and in the urinary bladders of animals prepared for chronic study. Lidocaine, 5–10 mg/kg, was injected intravenously either into the fetus or newborn lamb or into nonpregnant adult sheep. Serial samples of arterial blood and urine were obtained over four hours and analyzed for unchanged lidocaine using a gas chromatographic technique. The elimination half-lives of lidocaine in the bloods of nonpregnant ewe, neonate and fetus were 31, 51 and 33 min, respectively. Total-body clearances in the neonate and adult were 53 and 41 ml/min/kg. The metabolic clearances of lidocaine were the same in both, and approximated hepatic blood flow. Renal clearance was greater in the neonate, which was attributed to differences in urinary *p*H values and extents of protein binding. Thus, despite differences in half-lives, the newborn lamb is as capable as the adult of clearing lidocaine. (Key words: Anesthetics, local: lidocaine. Pharmacokinetics.)

CONSIDERABLE INFORMATION about the pharmacokinetics of various amide local anesthetic agents in adults is now available. However, there are relatively few data delineating the comparative pharmacokinetics of local anesthetic drugs in the fetus, newborn and adult. Recent reports indicate that the human newborn delivered during epidural anesthesia is capable of metabolizing lidocaine and excreting it in urine.[1] The objective of this study was to determine the dispositions of lidocaine in the fetus or newborn lamb, and in adult sheep, following a single intravenous injection of the drug.

* Associate Professor, Anesthesiology.
† Professor, Anesthesiology, Obstetrics and Gynecology.
‡ Assistant Professor, Anesthesiology.
§ Research Associate, Anesthesiology. Present address: Department of Anesthesiology, Tokyo University, Tokyo, Japan.
¶ Head, Drug Disposition.
** Head, Data Evaluation.
†† Scientific Director. Present address: Department of Anesthesiology, University of Massachusetts, School of Medicine, Worcester, Massachusetts 01605.

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Address reprint requests to Dr. Morishima.

Materials and Methods

This study involved ten pregnant ewes and their fetuses, seven newborn lambs, and seven nonpregnant ewes. Gestational ages of the fetuses ranged from 121 to 138 days (average 123 days). The newborns, all delivered vaginally at term, were one hour to two days old (average 29 hours). In preparation for the fetal investigations, pregnant ewes, deprived of food for 48 hours preceding the surgical procedure, were placed on an operating table in a semilateral position, following induction of low spinal anesthesia with tetracaine hydrochloride (6–9 mg). The uterus was exposed through a midline abdominal incision, hysterotomy was performed, and aminotic fluid was aspirated into a plastic syringe. The fetal end of the umbilical cord was partially exposed through the uterine incision, and the urachus cannulated with a polyethylene catheter, the tip of which was advanced into the bladder, using the technique described by Gresham *et al.*[2] Special care was taken to minimize handling of the cord in order to prevent constriction of the umbilical vessels. The umbilical cord was then replaced in the uterus. Subsequently, a fetal femoral artery and vein were catheterized through the same uterine incision. A polyethylene catheter was introduced into the amniotic cavity and the previously aspirated amniotic fluid was replaced after the uterine and abdominal walls had been closed. A maternal femoral artery and vein were also cannulated. All catheters were tunneled subcutaneously to the back of the ewe and secured in a plastic pocket sutured over the cutaneous stoma. Intravascular catheters were filled with aqueous heparin (1,000 U/ml) and refilled daily as long as the preparation was in use. When urine was not being collected, the urachal catheter was connected to the amniotic catheter for continuous drainage of the fetal bladder. All but two intrauterine studies were performed at least three days (range three to 23 days, average eight days) after the operation to allow for adequate recovery of the fetus.[2] In the remaining two preparations, experiments were performed 24 hours after the fetal operation in order to assess the validity of an acute surgical preparation in studying renal function of the fetus. In the newborn lambs and nonpregnant ewes, catheters were placed in the femoral artery and vein during local anesthesia with procaine.

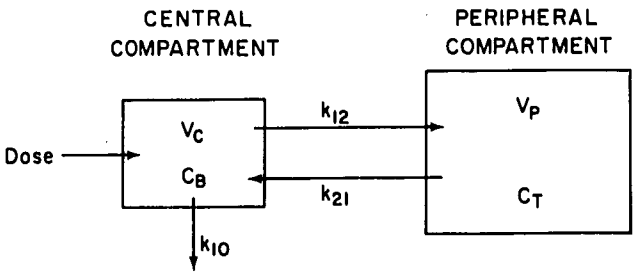

FIG. 1. Schematic representation of the two-compartment open model. C_B and C_T represent drug concentrations in blood and tissues, respectively. V_c and V_p represent apparent volumes of the central and peripheral compartments. k_{12} and k_{21} are rate constants of drug transfer between the central and peripheral compartments, and k_{10} is the rate constant for drug elimination from the central compartment.

The animals had their faces and eyes covered. They manifested no overt sign of agitation. In the nonpregnant ewes and most of the newborn lambs, the urinary bladder was cannulated through the urethra, but in some of the latter, via suprapubic incision. One fetus was delivered spontaneously with all catheters intact, 20 days after the fetal operation. In this preparation, three observations were made, the last one three days before birth, and another experiment was performed immediately after delivery.

Each study was preceded by a control period of one hour, during which the cardiovascular and acid–base state of the fetus or newborn lamb was considered satisfactory (table 1). Thereafter, lidocaine hydrochloride, 10 mg/kg (1 per cent concentration) was injected over a period of 60 sec into the femoral vein of the fetus or newborn lamb. Weight of the fetus was estimated on the basis of a composite curve of average weights of fetal lambs in relation to gestational age, prepared from two reported studies.[3,4] Lidocaine, 5 mg/kg, was administered to the nonpregnant ewes. All subjects were monitored during the control period, and for four hours after the injection of the drug. Arterial blood pressure and heart rate were measured and recorded continuously on a polygraph. Samples of arterial blood (1.0 ml) were obtained at predetermined intervals for four hours. In addition, in fetal studies, a sample of amniotic fluid was withdrawn simultaneously with the maternal and fetal blood samples. In all studies, specimens of urine were collected for periods ranging from 5 to 60 min. Blood samples were analyzed for *p*H, P_{CO_2}, and P_{O_2}; urine and amniotic fluid were analyzed for *p*H alone, using Radiometer microelectrodes and a Radiometer gas analyzer. Plasma was then separated by centrifugation and stored at −15 C, along with urine and amniotic fluid samples. All samples were subsequently analyzed for lidocaine concentration using a gas chromatographic technique that is highly specific and sensitive, measuring as little as 50 ng lidocaine per ml plasma or per gram of tissue.[5] The Student *t* test was used for statistical evaluation of the data.

Pharmacokinetic analysis of the data obtained from the newborn and from the nonpregnant ewe was performed utilizing a two-compartment model with elimination from the central compartment (fig. 1). This model was chosen because it is commonly used to describe biexponential decay curves of drug concentrations in plasma.[6] The best estimates of the pharmacokinetic parameters, V_c, k_{12}, k_{21}, k_{10}, were obtained with the nonlinear least-squares program NONLIN.[7] Each mean value of the pooled plasma data was weighted to the inverse of its variance for the computer fit. The hybrid rate constants, α and β, were calculated as functions of the rate constants k_{12}, k_{21}, and k_{10} ($\alpha + \beta = k_{12} + k_{21} + k_{10}$ and $\alpha\beta = k_{10}k_{21}$). Note that α and β describe the drug decay curve in plasma. α pertains to the initial rapid fall in plasma concentration, mainly due to drug distribution from central to peripheral compartment, while β describes the slower "elimination" phase of the curve. The distribution and elimination half-lives were derived from the following

TABLE 1. Mean (± SE) Values for Heart Rate, Blood Pressure, Blood *p*H and Gases in Fetal and Newborn Lambs Prior to and Four Hours after Intravenous Administration of Lidocaine

	Heart Rate (Beats/Min)	Mean Arterial Pressure (torr)	pH_a	Pa_{CO_2} (torr)	Base Deficit (mEq/l)	Pa_{O_2} (torr)	Urinary *p*H	Amniotic Fluid *p*H
Fetal lambs (n = 8)								
Control	170 ± 6.3	43 ± 2.0	7.38 ± 0.012	43 ± 2.0	0.4 ± 1.00	18 ± 1.0	6.74 ± 0.016	6.91 ± 0.098
End*	183 ± 7.4	42 ± 2.1	7.37 ± 0.006	43 ± 1.4	0.5 ± 0.89	18 ± 0.5	6.62 ± 0.177	7.04 ± 0.095
Newborn lambs (n = 7)								
Control	187 ± 10.3	69 ± 2.5	7.40 ± 0.001	37 ± 2.0	2.2 ± 0.94	86 ± 3.2	6.08 ± 0.815	
End*	185 ± 12.2	70 ± 2.4	7.40 ± 0.024	40 ± 1.2	1.2 ± 2.4	84 ± 4.1	6.07 ± 0.176	

* Four hours after administration of lidocaine.

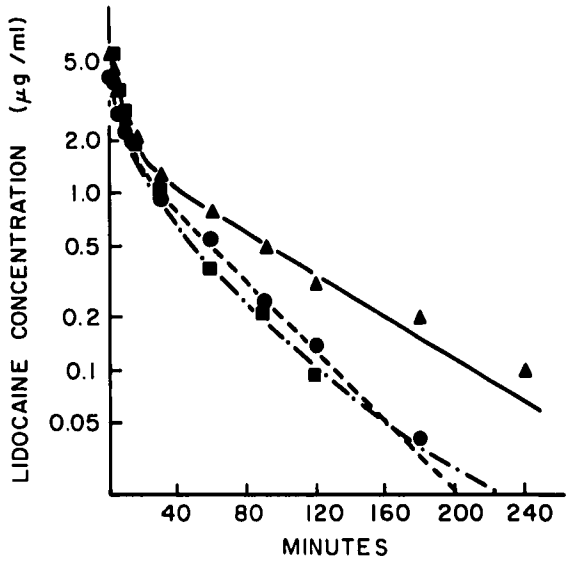

FIG. 2. Lidocaine concentrations (base) in arterial blood following an iv bolus: ■, fetus, and ▲, newborn, following 10 mg/kg lidocaine; ●, nonpregnant adult, 5 mg/kg lidocaine.

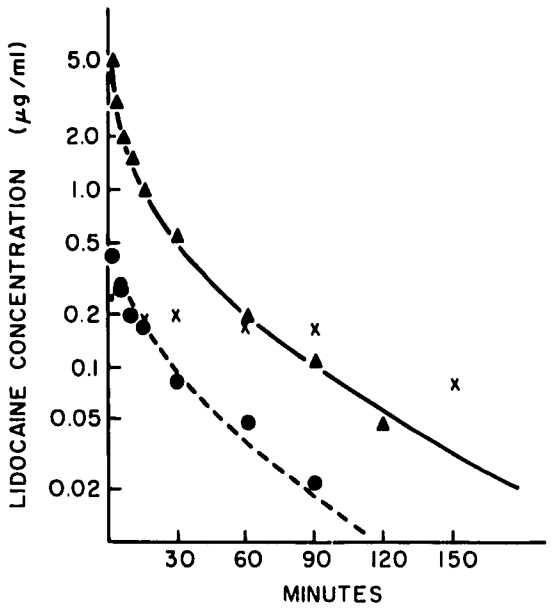

FIG. 3. Lidocaine concentrations (base) following administration of 10 mg/kg lidocaine to the fetus: ▲, fetal arterial level; ●, maternal arterial level; +, amniotic fluid level.

formulas:

$$t_{1/2\alpha} = \frac{0.693}{\alpha}$$

$$t_{1/2\beta} = \frac{0.693}{\beta}$$

Area under the plasma concentration curve (AUC) was calculated using trapezoid approximation. Clearance is reported as the product of k_{10} and V_c. Only $t_{1/2\beta}$ (calculated by log-linear regression) and AUC were determined for the fetal and maternal blood levels of lidocaine.

Renal clearance was calculated by dividing the amount of lidocaine excreted in the urine in 240 min by the AUC to 240 min.

Results

Peak arterial blood concentrations of lidocaine occurred 1 min after the end of injection. They amounted to an average of 4.43 μg/ml (±1.00 SE) in the adult, 6.22 μg/ml (±0.58) in the newborn, and 5.06 μg/ml (±0.34) in the fetus. There were rapid declines in blood levels of the drug over the next 15 min to a mean of 2.01 μg/ml (±0.32) in the adult, 2.07 μg/ml (±0.26) in the neonate, and 0.67 μg/ml (±0.19) in the fetus (fig. 2; table 2). Thereafter, blood levels of lidocaine decreased more slowly, to the lowest detected values of 0.04 μg/ml (±0.01) in the adult (at 180 min), 0.10 μg/ml (±0.04) in the neonate (at 240 min), and 0.05 μg/ml (±0.01) in the fetus (at 120 min). Lidocaine was detectable in maternal blood as early as 2 min after the end of fetal injection, with a mean value of 0.43 μg/ml (±0.06), indicating very rapid equilibration between the fetus and the mother (fig. 3).[8] The maternal blood levels decayed in a manner parallel to those in the fetus from 20 min on. Figures 2 and 3 include computer-simulated curves generated on the basis of optimized values of pharmacokinetic indices. The correlations between the observed and computer-predicted blood levels were 0.994 and 0.998 for the nonpregnant ewe and the newborn, respectively.

The elimination half-life of lidocaine was approximately 60 per cent longer in the newborn than in the

TABLE 2. Lidocaine Concentrations in Arterial Blood (Mean ± SE)

Time (Min)	Lidocaine (μg/ml)			
	Adult	Neonate	Fetus	Mother
1	4.43 ± 1.00	6.22 ± 0.58	5.06 ± 0.34	— —
2	4.30 ± 0.82	5.09 ± 0.33	3.09 ± 0.40	0.43 ± 0.06
5	2.81 ± 0.60	3.95 ± 0.47	1.93 ± 0.32	0.28 ± 0.04
10	2.22 ± 0.46	2.71 ± 0.22	1.39 ± 0.30	0.19 ± 0.04
15	2.01 ± 0.32	2.07 ± 0.26	0.67 ± 0.19	0.16 ± 0.03
30	0.93 ± 0.18	1.29 ± 0.16	0.53 ± 0.11	0.08 ± 0.01
60	0.53 ± 0.19	0.77 ± 0.17	0.19 ± 0.06	0.05 ± 0.02
90	0.25 ± 0.06	0.49 ± 0.15	0.11 ± 0.02	0.02 ± 0.01
120	0.14 ± 0.04	0.32 ± 0.09	0.05 ± 0.01	
180	0.04 ± 0.01	0.20 ± 0.09		
240		0.10 ± 0.04		

adult (51 *vs.* 31 min) (table 3). The distribution half-lives were approximately 5 min in both. When the elimination half-life was calculated on an individual basis, the average $T_{1/2\beta}$ for the adult was 32 min (range 30–37 min) and that for the newborn was 50 min (range 30–78 min). On a weight basis, the total-body clearance was approximately 25 per cent larger in the newborn than in the adult. Each of the theoretical volumes of distribution was 40 to 100 per cent larger in the newborn on a per-kilogram basis.

Unmetabolized lidocaine was readily detected in both fetal and newborn urine within 5 min of the injection, with mean concentrations of 2.1 and 57.1 μg/ml, respectively. While the renal clearance remained constant after the first 15 min, the rate of renal excretion of lidocaine was maximal during the first 15 min in all instances and decreased thereafter (table 3; fig. 4).

Lidocaine was also detected in the amniotic fluid (fig. 3), in much lower peak concentrations (0.2 μg/ml at 30 min) than those found in either fetal blood or urine. No measurable amount was found in the amniotic fluid obtained after 150 min.

A decrease in the urinary output occurred in the fetus following injection of the drug, from the mean control value of 0.21 ± 0.052 ml/kg/min to 0.17 ± 0.021 ml/kg/min during the first 15 min, and to 0.15 ± 0.022 ml/kg/min at 30 min. Although these changes were not statistically significant, the urinary volume remained below control throughout the experiment. In the newborn, the control value was 0.17 ± 0.045 ml/kg/min, with a tendency towards a decrease in urinary output after administration of lidocaine; the lowest urinary output obtained was 0.11 ± 0.023 ml/kg/min, at 30 min; it remained between 0.13 and 0.15 ml/kg/min thereafter. Again, these changes were not statistically significant. No change in urinary output was observed after injection of lidocaine into the adult sheep, the average value remaining 0.16 ml/kg/min.

Alterations in acid–base state, blood pressure, and heart rate were minimal in all experiments (table 1). Transient but significant ($P < 0.05$) bradycardia and hypertension occurred in all fetuses ¼ to 1 min following the completion of lidocaine injection. In the ewes, a brief period of marked tachycardia occurred in association with hypertension ($P < 0.01$). These changes lasted less than 5 min.

Although the animals from the two fetal experiments performed on the first postoperative day appeared to be in good condition, as judged by acid–base, arterial pressure, and heart rate values, a significantly high urinary *p*H (7.9 *vs.* 6.7 in chronic preparations) was found during the control period. Following the injection, concentrations of lidocaine in the fetal blood were comparable to those in chronic preparations, but unusually decreased urinary output and renal excretion of the drug were found.

Discussion

These experiments have shown that in the metabolic and physiologic disposition of lidocaine adult and newborn sheep have both similarities and differences. Surprisingly, total-body clearance was about 20 per cent greater in the newborn than in the adult. Metabolic clearance can be calculated by subtracting renal clearance from total-body clearance. Metabolic clearances, presumably hepatic, were very similar in the newborn and the adult (43 and 40 ml/min/kg), and very nearly equal to hepatic blood flow.[9] Since all animals were offered food and water *ad libitum* before and throughout the experiment, a starvation-induced decrease in blood flow to the liver would not be expected. These data indicate that, at least in the sheep, the neonate is just as efficient as the adult in metabolizing lidocaine.

The volume of distribution and renal clearance were considerably greater in the neonate. This may have been related to decreased plasma protein binding. Although no pertinent data for sheep exist, the plasma binding of lidocaine in the human neonate is approximately 50 per cent of that in the adult.[10] Consistent with the larger volume of distribution is the finding in maternal and fetal guinea pigs that, in the organs studied, the tissue-to-plasma concentration ratio was greater in the fetus.[11] In most species, renal clearance of lidocaine comprises less than 5 per cent of total-

TABLE 3. Pharmacokinetic Indices

	Lidocaine (mg/kg)	V_c* (l/kg)	$V_d\beta$† (l/kg)	Total-body Clearance (ml/min/kg)	Half-life (Min)		Dose/AUC‡ (ml/min/kg)	Urinary *p*H	Renal Clearance (ml/min/kg)
					α	β			
Adult	5	.9	1.84	41.2	5.0	30.9	39.2	6.4	1.01
Newborn	10	1.42	3.94	53.5	5.0	51.0	50.4	6.1	9.21
Fetus	10					33.0	139.0	6.7	1.51
Maternal						33.0	41.3		

* V_c = volume distribution, central compartment.
† $V_d\beta$ = clearance/β = (k_{10}/β) (V_c).
‡ AUC = area under the plasma concentration curve.

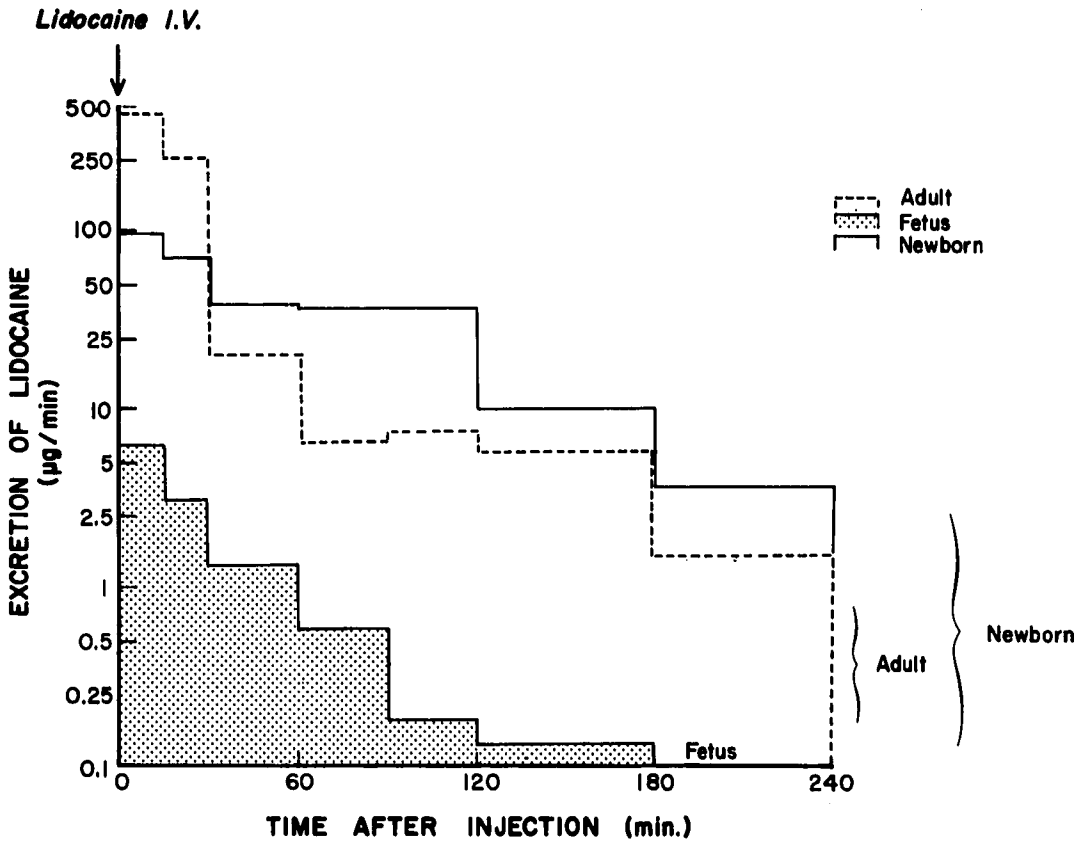

FIG. 4. Comparative renal excretions of lidocaine in adult, fetal, and newborn sheep following administration of 5–10 mg/kg, iv.

body clearance. However, in the newborn lamb, renal clearance contributed 17 per cent of total-body clearance. This is somewhat surprising, since renal function (filtration rate and active secretion) is not usually considered to be fully developed in the neonate. The urinary *p*H of the neonate was lower than that of the adult, which would partly explain the difference. In man, the renal clearance of lidocaine changed by a factor of two, with the urinary *p*H change of 0.4 *p*H units.[12] Decreased plasma protein binding could also contribute to the elevated renal clearance. The difference between renal clearances in the neonate and fetus can be attributed to the large difference between urinary *p*H values (6.08 *vs.* 6.7) (table 1). The differences in clearance and volume of distribution might be less if they were normalized to surface area rather than body weight.

Despite its greater clearance in the neonate, the half-life of lidocaine in the neonate is longer than that in the adult. This is most probably due to its larger distribution volume and not to a deficient drug-metabolizing system. Note that half-life is a function of both volume of distribution and clearance: $t_{1/2} = .693 \times V_d/\text{clearance}$. Because of the larger distribution volume, a smaller fraction of the drug is available to the clearing organ at any one time, and hence, the rate of elimination is slower. The half-lives of many drugs, including phenytoin, nortriptyline, salicylate, and amobarbital, appear to be prolonged in the infant.[13] It is easy to speculate that this may not be due solely to differences in clearance, but that distribution differences may also play a role.

The elimination half-lives in both fetal and maternal blood were 33 min, which is only slightly longer than the half-life in the blood of the nonpregnant adult. The half-life in the fetus was considerably shorter than that in the newborn. Obviously, this does not mean that the fetus is metabolizing the drug faster than the neonate. Rather, it is in equilibrium with the maternal system, as theoretically all the maternal tissues should be equilibrated with blood during the β-elimination phase. The maternal rate of metabolism is now the controlling factor, since the absolute value of its clearance is overwhelmingly greater than that of fetal clearance. That the peak maternal blood level occurs in less than 2 min is also indicative of rapid equilibration.

The "apparent" total-body clearance (dose/AUC) (table 3) was much greater in the fetus than in either the newborn or the nonpregnant adult. Placental

transfer was probably responsible for this difference. The maternal–fetal mass difference will dictate almost exclusively a one-way placental transfer. This apparent clearance is within physiologic expectations, since umbilical flow in the sheep has been reported to be 230 ml/min/kg.

The low levels of lidocaine found in amniotic fluid represent sources other than fetal urine, since it was removed almost completely from the bladder throughout the experiment via the indwelling catheter. The epithelium of the amniotic sac and fluid excreted through the fetal airways might be such sources.

In conclusion, the neonate, and probably the fetus, are proficient in lidocaine metabolism. However, the dominant factor in fetal lidocaine clearance still appears to be placental transfer. Placental metabolism cannot be ruled out. However, it does not appear to be very important, since 95 per cent of the drug injected into the fetus could be accounted for by maternal levels (when the AUC values for the pregnant and nonpregnant adults were normalized for dose).

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References

1. Blankenbaker WL, DiFazio CA, Berry FA Jr: Lidocaine and its metabolites in the newborn. ANESTHESIOLOGY 42:325–350, 1975
2. Gresham EL, Rankin JHG, Makowski EL, et al: An evaluation of fetal renal function in a chronic sheep preparation. J Clin Invest 51:149–156, 1972
3. Huggett A StG, Widdas WF: The relationship between mammalian foetal weight and conception age. J Physiol (Lond) 114:306-317, 1951
4. Metcalfe J, Meschia G, Hellegers A, et al: Observations on the growth rates and organ weights of fetal sheep at altitude and sea level. Q J Exp Physiol 47:305–313, 1962
5. Keenaghan JB: The determination of lidocaine and prilocaine in whole blood by gas chromatography. ANESTHESIOLOGY 29: 110–112, 1968
6. Greenblatt DJ, Koch-Weser J: Drug therapy—clinical pharmacokinetics. N Engl J Med 293:702–705, 1975
7. Metzler CM, Elfring GL, McEwen AJ: A User's Manual for NONLIN and Associated Programs. Upjohn Co., Kalamazoo, Michigan, April 20, 1974
8. Morishima HO, Adamsons K: Placental clearance of mepivacaine following administration to the guinea pig fetus. ANESTHESIOLOGY 28:343–348, 1967
9. Katz ML, Bergman EN: Simultaneous measurements of hepatic and portal venous blood flow in the sheep and dog. Am J Physiol 216:946–952, 1969
10. Tucker GT, Boyes RN, Bridenbaugh PO, et al: Binding of anilide-type local anesthetics in human plasma. II. Implications *in vivo*, with special reference to transplacental distribution. ANESTHESIOLOGY 33:304–314, 1970
11. Finster M, Morishima HO, Boyes RN, et al: The placental transfer of lidocaine and its uptake by fetal tissues. ANESTHESIOLOGY 36:159–163, 1972
12. Eriksson E: Prilocaine: An experimental study in man of a new local anesthetic with special regards to efficacy, toxicity and excretion. Acta Chir Scand (suppl) 358:63, 1966
13. Horning MG, Butler CM, Nowlin J, et al: Drug metabolism in the human neonate. Life Sci 16:651–672, 1975