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Lidocaine and Its Metabolites in the Newborn

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Concentrations of lidocaine and its metabolites were measured chromatographically in the blood and urine of mothers and babies after epidural administration of lidocaine to the mother for cesarean delivery. Delivery occurred a mean time of 29.83 ± 8.64 minutes after a mean dose of 398.33 ± 63.38 mg to the mother, at which time mean maternal venous plasma concentration was 2.79 ± 1.03 μg/ml. while mean newborn mixed cord plasma concentration was 1.70 ± 0.77 μg/ml. Of the total molar quantity of lidocaine and metabolite recovered from the newborns' urine in the first 12 hours of life, 50.63 per cent appeared as unchanged lidocaine, while 49.37 per cent appeared as metabolites. In the second 12 hours of life, 23.37 per cent appeared as unchanged lidocaine, while 76.63 per cent appeared as metabolites. We conclude that the greater proportion of metabolite excretion in the second 12 hours is evidence that the newborn is capable of metabolizing lidocaine. (Key words: Anesthetics, local, lidocaine; Biotransformation, lidocaine; Anesthesia, obstetric; Age factors, lidocaine metabolism.)

IT IS WELL KNOWN that lidocaine and other local anesthetics administered to obstetric patients during labor and delivery cross the placental membrane and enter the fetal circulation.[1-7] These agents must then be either metabolized or excreted unchanged by the newborn. Whether or not the neonate can metabolize local anesthetic agents may play a significant role in determining the course of fetal drug depression.

Shnider[2] measured plasma lidocaine decay in the mother and fetus following delivery. He found the decay slopes to be similar, and suggested that the newborn distributed, metabolized, or excreted lidocaine at approximately the same rate as the mother. However, several studies suggest that drug metabolism occurs more slowly in newborn animals and man. Jondorf[8] reported that newborn mice and guinea pigs lacked the oxidative and conjugative enzymatic mechanisms for metabolizing drugs during the first 24 hours after birth. Similarly, Meffin[9] observed that mepivacaine metabolism by the human neonate was markedly slower in comparison with that of normal adult man. Further evidence of less active drug metabolism in the neonate has been seen after tolbutamide[10] and acetanilide[11] administration. Direct evidence of the metabolism of lidocaine by the human newborn is lacking.

This study was designed to evaluate the metabolism of lidocaine in the human newborn by observing the urinary excretion patterns of lidocaine and its metabolites of newborns whose mothers had received epidural lidocaine anesthesia.

Method

Epidural anesthesia with lidocaine, 1.5 per cent, with epinephrine 1:200,000, was administered to six healthy parturients undergoing cesarean section for cephalopelvic disproportion or elective repeat cesarean delivery. Control samples of maternal venous blood and urine were obtained prior to lidocaine administration. Samples of maternal blood and urine and mixed cord blood were obtained at the time of delivery. In addition, urine samples were collected from the newborn during the first and second 12 hours after birth. Blood was collected in 10-ml samples, with prompt separation of the plasma for freezing. Urine was collected from the newborns with Hollister bags as first and second 12-hour specimens and frozen. There were large variations both in the volumes of urine collected from the same infant during two collection periods and in the total volumes collected from individual babies.

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These variations could have resulted from different states of hydration, from different bladder-emptying patterns resulting in voiding just prior or subsequent to the end of a collection period, or from loss of urine. The Hollister bags were applied immediately after birth as soon as the babies were determined to be stable by an examining pediatrician. Babies who were known to have voided during this interval were excluded from the study, as were babies in whom there was leakage from the bags due to unsatisfactory adhesion. The possibility of inaccurate urine volumes because of the collection technique could have been avoided only by the insertion of indwelling urinary catheters, a procedure which was felt to be unjustified.

All specimens were analyzed by gas chromatography for lidocaine (XY), monoethylglycine xylidide (MEGX), glycinexylidide (GX), dimethyl aniline (DMA), and parahydroxyxylidide (POHX). Chromatographic quantitation was achieved with a Hewlett-Packard 5750 gas chromatograph equipped with a flame ionization detector and a 2 mm, 6-foot glass column containing 10 per cent UCW 98 on Chromosorb W AWHP. The technique for measuring the first three compounds has been reported.[12] Analysis of two other metabolites (POHX and DMA) was carried out as follows. One milliliter of urine or plasma was buffered to *p*H 4.5 with 2 ml of acetate buffer and the resultant mixture was treated with approximately 3 mg of glucuronidase containing sulfatase (Sigma Chemical Co.) for 3 hours at 37 C. The mixture was then adjusted to *p*H 8–9 by careful addition of sufficient quantities of .3 N ammonium hydroxide and double-extracted with 10 ml of chromatographic-grade chloroform. The chloroform solution was evaporated at 35 C under vacuum with a Buchler evaporator to approximately 25 μl. The material was then chromatographically assayed using a temperature program from 120 to 200 C at a 15-degree/min temperature rise after a 4-min post-injection delay. Carbocaine was used as the internal standard.

The concentration range of linearity for the detector for the POHX was established over a range of 0.03 to 30 μg, and mean recoveries from 0.2 to 3 ml of water and plasma were found to be 82.7 and 72.7 per cent. Glucuronide hydrolysis was observed to be maximal after 2 hours; however, after 4 hours a gradual loss of POHX became evident. Meticulous care of the *p*H of the final solution extracted is essential, for if *p*H becomes greater than 9, POHX recovery is markedly reduced and the balance of the material is irretrievably lost.

The method used will also identify the metabolite, DMA. Detector response for DMA was observed to be linear from 0.27 to 45 μg, and recovery from 3 ml of water was found to be 74.5 per cent at *p*H 9 and 85.7 per cent at *p*H 12. However, while all samples were analyzed for DMA, none was found.

Results

Table 1 shows the concentrations of lidocaine and metabolites found in maternal venous plasma and urine and in mixed cord plasma at the time of delivery, which occurred a mean time of 29.83 ± 8.64 minutes after a mean epidural dose of 398.33 ± 63.38 mg lidocaine. Neither lidocaine nor metabolites were found in any control samples, and thus these data are omitted from the table. At delivery, the mean maternal venous plasma concentration was 2.79 ± 1.03 μg/ml, while the newborn mixed cord plasma concentration of lidocaine was 1.70 ± 0.77 μg/ml. Concentrations in the newborns' urine during the first and second 12 hours after birth are also shown in table 1.

Since all newborns had divided first and second 12-hour urine specimens of known volume, molar quantities of each compound excreted were calculated (table 2). The amounts of unchanged lidocaine excreted in the second period decreased in all babies. In four of six babies, the amounts of metabolites also decreased. The ratio of total moles of metabolite to total moles of unchanged lidocaine was calculated for each newborn for each of the two urine-collection periods. These ratios (table 2) indicate a fourfold increase in excretion of metabolites compared with unchanged lidocaine in the second 12 hours.

The data also demonstrate that unchanged lidocaine accounted for 45.11 ± 17.20 per cent of the drug recovered from infants in the first 24 hours of life.

TABLE 1. Lidocaine and Metabolites in Cesarean Section Patients

	Epidural Lidocaine Dose (mg)	Time of Delivery after Lidocaine (Min)	Compound*	Maternal Concentration at Delivery (μg/ml)		Newborn Concentration (μg/ml)		
						Mixed Cord Plasma at Delivery	Urine	
				Venous Plasma	Urine		0–12 hr	12–24 hr
Patient 1	400	30	Lidocaine	3.76	6.77	1.62	1.97	0.43
			MEGX	1.35	14.94	0.81	1.02	0.61
			POHX	0.10	38.47	0.08	0.05	1.34
Patient 2	400	23	Lidocaine	1.76	9.38	0.85	2.18	0.19
			MEGX	0.37	0.96	0.28	2.42	0.72
			POHX	0.45	15.15	0.45	0.54	0.39
Patient 3	400	33	Lidocaine	2.11	16.99	1.79	10.46	1.04
			MEGX	1.15	5.46	0.41	2.05	0.38
			POHX	0.37	16.02	0.19	0.86	0.08
Patient 4	510	41	Lidocaine	3.39	5.36	2.11	3.39	0.89
			MEGX	0.72	4.78	0.95	4.55	0
			POHX	0.48	26.02	0.32	1.10	1.98
Patient 5	320	35	Lidocaine	3.97	51.17	2.92	29.32	4.14
			MEGX	1.51	0.80	0.79	13.93	4.33
			POHX	0.56	1.15	0.64	0.20	4.75
Patient 6	360	17	Lidocaine	1.77	1.92	0.93	0.98	0.22
			MEGX	1.89	0.19	0.37	0.63	0.54
			POHX	0.71	14.34	0.46	0.65	1.02

* MEGX = monoethylglycine xylidide; POHX = parahydroxyxylidide.

Discussion

Many obstetricians and anesthetists favor conduction anesthesia in obstetrics because of the concept that local anesthetics administered to the mother have only indirect effects on the fetus or newborn. However, the fact that local anesthetics do cross the placenta and the fact that elevated fetal concentrations are associated with undesirable effects on the newborn are well documented. Shnider[2] has shown a significant decrease in 1-minute Apgar scores in infants having lidocaine levels greater than 2.5 μg/ml. The lower toxic level for the newborn compared with the 5 μg/ml toxic plasma lidocaine level reported by Foldes[13] for adult man may be explained by the decreased protein binding of lidocaine by fetal plasma found by Tucker.[7]

Shnider[1] found that the decay slopes of lidocaine measured in maternal and newborn blood were similar, and suggested that the infant distributed, metabolized, or excreted lidocaine at approximately the same rate as the mother. However, the ability of the newborn to metabolize drugs has been found to be deficient by many investigators. O'Donoghue[14] administered small doses of meperidine, chlorpromazine, and promazine to newborns and found that conjugated metabolites that appeared in the urine of infants whose mothers had received the same drugs before delivery did not appear in the urine of neonates to whom the drugs were administered after delivery. He therefore concluded that the babies lacked conjugative mechanisms for biotransformation of the drugs studied. Nitowsky[10] and Vest[11] have demonstrated that the human newborn can metabolize drugs by various enzymatic routes, although at a decreased rate, during the first 24 hours of life. Meffin[9] has examined the metabolism of mepivacaine in the human adult and neonate, but was ham-

TABLE 2. Molar Quantities of Lidocaine and Metabolites in Urine of Newborns

	Compound*	Newborn Urine 0–12 Hours			Newborn Urine 12–24 Hours			Per Cent of Total Excretion during first 24 Hours
		Nanomoles	Per Cent of Total	Ratio of Metabolites/ Lidocaine	Nanomoles	Per Cent of Total	Ratio of Metabolites/ Lidocaine	
Patient 1	Lidocaine	599	61.2		62	12.7		45.0
	MEGX	352	36.0	0.634	99	20.2	6.874	30.7
	POHX	27	2.8		329	67.1		24.3
Patient 2	Lidocaine	168	37.3		6	11.3		34.6
	MEGX	211	46.9	1.691	26	49.1	7.850	47.1
	POHX	71	15.8		21	39.6		18.3
Patient 3	Lidocaine	402	73.4		11	62.8		73.0
	MEGX	90	16.4	0.360	5	28.6	0.592	16.8
	POHX	56	10.2		1.5	8.6		10.2
Patient 4	Lidocaine	674	32.5		43	20.9		26.7
	MEGX	27	49.5	2.080	0	0.0	3.785	24.8
	POHX	373	18.0		1,630	79.1		48.5
Patient 5	Lidocaine	3,258	64.4		283	24.1		56.9
	MEGX	1,758	34.8	0.553	336	28.6	3.149	33.6
	POHX	38	0.8		555	47.3		9.5
Patient 6	Lidocaine	275	35.0		1.2	8.4		34.47
	MEGX	201	25.5	1.857	3.4	23.8	10.950	25.51
	POHX	311	39.5		9.7	67.8		40.02
MEAN	Lidocaine		50.63 ± 17.72			23.37 ± 20.22		45.11 ± 17.20
	MEGX		34.85 ± 12.56	1.19 ± 0.76		25.05 ± 15.85	5.53 ± 3.72	29.75 ± 10.27
	POHX		14.52 ± 14.01			51.58 ± 25.58		25.14 ± 16.02

* MEGX = monoethylglycine xylidide; POHX = parahydroxyxylidide.

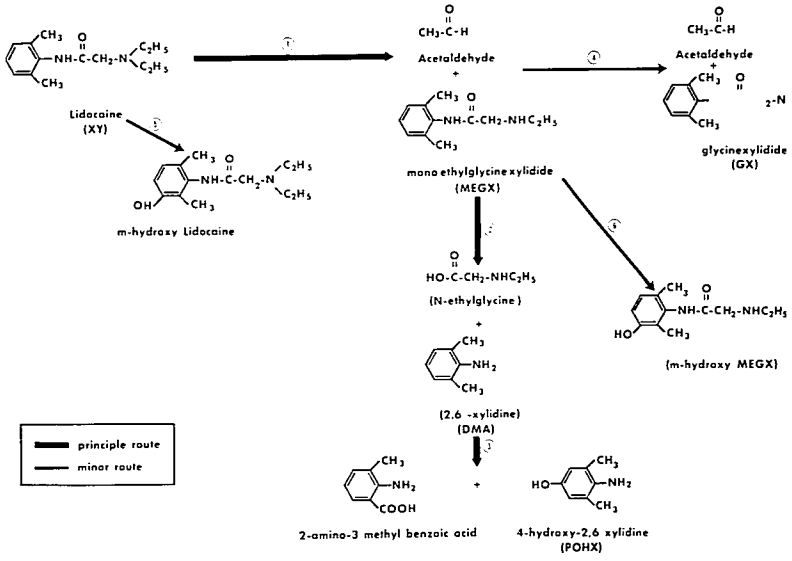

FIG. 1. Summary of known pathways of the metabolism of lidocaine by man. Bold arrows indicate the principal pathway.

pered, as we were, by being unable to give the drug directly to the neonate for nontherapeutic purposes. The mepivacaine metabolites found in the neonate's urine could not be unequivocably attributed to metabolism of mepivacaine by the neonate rather than to placental passage from the mother.

In our study, we demonstrated evidence of lidocaine metabolism by the newborn by finding that the ratio of metabolites to unchanged lidocaine in the urine was higher in the second 12 hours of life than in the first 12 hours. The variation of lidocaine and metabolite levels in the cord plasma and neonate's urine could have resulted from variable rates of drug metabolism by the mother or the fact that drug-metabolizing enzymes in the neonate are probably saturable and have different kinetic rates.

The known pathways of lidocaine metabolism are summarized in figure 1. The major pathway is oxidative de-ethylation to MEGX, subsequent amidase hydrolysis to DMA, then aromatic hydroxylation to POHX, and finally conjugation of POHX. In our study, all samples of both maternal and cord plasma contained XY, MEGX, and POHX, with concentrations of XY and MEGX in the cord plasma being roughly 55 per cent of those in the maternal plasma. This is in agreement with the transplacental gradient for lidocaine reported by Shnider[1] and others. We found, however, that the cord plasma POHX concentration was 80 per cent of that in the maternal plasma. This significant difference could be explained by the possibility of differential binding of metabolites in maternal and fetal plasma, similar to the differential binding of lidocaine and

bupivacaine by maternal and fetal plasma found by Tucker,[7] or possibly by POHX traversing the placental membrane more readily than XY and MEGX.

In comparing total molar quantities of lidocaine and metabolite excretion by the newborn in the first and second 12 hours, we found lidocaine and MEGX decreased in the second period in all babies, while POHX increased in three of the six. Lidocaine excretion decreased to a greater extent than excretion of MEGX, so that the sum of the metabolites MEGX and POHX compared with unchanged lidocaine (shown as a ratio of metabolites to lidocaine in table 2) increased fourfold in the second 12 hours of life. We believe this to be conclusive evidence that metabolism of lidocaine occurs in the newborn.

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