The Placental Transfer of Lidocaine and Its Uptake by Fetal Tissues

Mieczyslaw Finster, M.D.,* Hisayo O. Morishima, M.D., Ph.D.,†
Robert N. Boyes, Ph.D.,‡ Benjamin G. Covino, Ph.D., M.D.§

The distribution of lidocaine in tissues was studied in fetal guinea pigs following iv injection into the mother (10 mg/kg). Drug concentrations in maternal and fetal blood, liver, heart, brain, and kidney and in the placenta were measured, using a gas chromatographic technique. Relatively high concentrations were found in the fetal liver, heart, and brain, indicating that rapid placental transfer of this drug was paralleled by its rapid uptake into highly perfused fetal tissues. The liver was the only organ in which lidocaine concentrations in the fetuses exceeded those in the mothers. Myocardial levels in the fetus could account for the susceptibility of the fetal heart to local anesthetics administered to the mother. Placental uptake of lidocaine was low, indicating that, unlike the fetal liver, the placenta plays a limited role in decreasing the drug concentration in fetal blood before it reaches vital organs such as the heart and brain. (Key words: Lidocaine; Blood concentrations; Tissue concentrations; Guinea pig fetus; Gas chromatography.)

LOCAL ANESTHETICS administered for regional anesthesia in obstetrics are rapidly absorbed into the maternal blood and transmitted across the placenta.[1-4] Except in the case of spinal anesthesia, relatively large doses are necessary, and these occasionally result in high blood levels in the fetus and neonatal depression.[1, 3] Paracervical blocks, in particular, expose the

fetus to the risk of overdose, because of the extreme rapidity with which these drugs are absorbed from the broad ligament.[4] The fetal bradycardia and acidosis that frequently follow[5, 6] coincide with elevated drug concentrations in fetal blood.[3, 4] Consequently, some authors have attributed these changes in fetal condition to direct myocardial depression by local anesthetics.[4, 6] Furthermore, three perinatal deaths have been ascribed to local anesthetic intoxication of the fetus following cervical block.[7, 8] This study was undertaken to determine uptake of lidocaine by the myocardium and other tissues of guinea pig fetuses after its administration to the mothers.

Material and Methods

Pregnant guinea pigs at term received a slow iv injection (over approximately a minute) of lidocaine, 1 per cent, 10 mg/kg, into an exposed forelimb vein. They were stunned and killed by immersion in liquid nitrogen 1, 2, 5, 10, 15, or 25 minutes following the end of injection. After a brief period of rewarming to facilitate dissection, the fetuses were removed through an abdominal incision. Maternal and fetal blood samples were obtained from the hearts, and the following fetal and maternal organs were sampled: brain, liver, heart, kidney, and placenta. Twenty-three mothers and 91 fetuses were studied, at least three mothers and nine fetuses for each time interval.

All samples were analyzed for lidocaine content using a gas chromatographic technique. Samples of maternal and fetal tissues were weighed and transferred to a homogenizer cup, to which a measured quantity of internal standard solution of methyl-ethyl lidocaine in distilled water was added. The mixture was homogenized. The subsequent extraction procedure and gas chromatographic assay for lidocaine were carried out as described previously

* Associate Professor of Anesthesiology, College of Physicians and Surgeons.
† Assistant Professor of Anesthesiology, College of Physicians and Surgeons.
‡ Head, Drug Disposition Section, Astra Pharmaceutical Products, Inc.
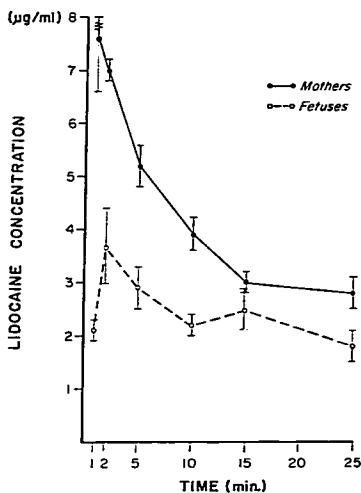§ Scientific Director, Astra Pharmaceutical Products, Inc.

FIG. 1. Mean lidocaine concentrations in the maternal and fetal blood. Each point on the curves corresponds to at least three mothers or nine fetuses. The vertical lines indicate standard error of the means.

for blood.[9] This procedure was specific for unchanged lidocaine, since the retention time for the drug was 15 minutes, whereas the retention times of the two most likely metabolites, monoethyl glycinexylidide and glycinexylidide, were 11 and 14 minutes, respectively.

Blood and tissue level data were analyzed for statistical significance by successive one-way analyses of variance for independent groups. Where F ratios were significant (α = 0.05), t tests were carried out on individual data sets.

Results (Figures 1 to 6)

Mean lidocaine concentrations in maternal and fetal blood are shown in figure 1. The peak maternal concentration, 7.6 μg/ml, occurred at 1 minute; the concentration then de-
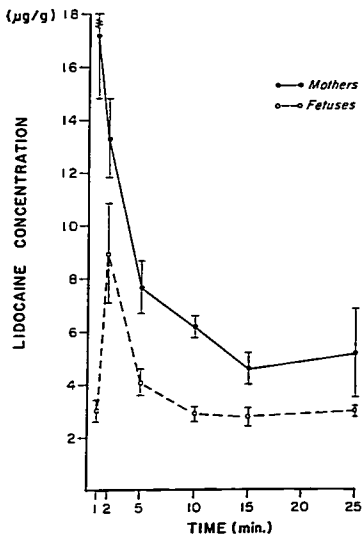

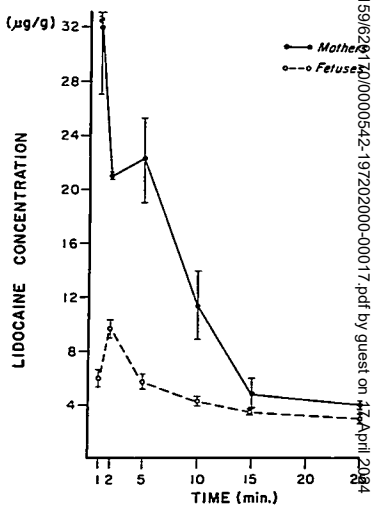FIG. 2. Mean lidocaine concentrations in the maternal and fetal myocardium.

FIG. 3. Mean lidocaine concentrations in the maternal and fetal brain.

clined to 2.8 μg/ml at 25 minutes. The maximum fetal blood level, 3.6 μg/ml, reached at 2 minutes, was 51 per cent of the mean maternal level at that time (fig. 6). The rate of decline in fetal blood concentrations was somewhat slower than that in the mothers. Indeed, the mean fetal blood levels had decreased to 2.2 μg after 10 minutes and did not change significantly after 15 and 25 minutes (10 vs. 15 minutes, $P > 0.4$; 10 vs. 25 minutes, $P > 0.2$; 15 vs. 25 minutes, $P > 0.1$).

Mean lidocaine concentrations in maternal and fetal myocardiums were higher than those in blood (figs. 2 and 6). In the mother a peak concentration of 17.2 μg/g was reached at 1 minute. The subsequent decline was rapid until 5 minutes after the injection. Values after 10, 15, and 25 minutes were not significantly different from each other (10 vs. 15 minutes, $P > 0.05$; 10 vs. 25 minutes and 15 vs. 25 minutes, $P > 0.5$). Mean concentrations in fetal myocardium rose from 3.0 μg/g at 1 minute to 8.9 μg/g, representing 68

Fic. 5. Mean lidocaine concentrations in the maternal and fetal liver.

per cent of the maternal level, at 2 minutes. At that time, the difference between mean maternal and fetal values was not significant (0.1 $> P > 0.05$). Between 2 and 5 minutes fetal levels declined rapidly to 4.1 μg/g. Between 10 and 25 minutes they remained almost unchanged at approximately 3.0 μg/g. After 25 minutes, the difference between mean maternal and fetal values was again not significant (0.3 $> P > 0.2$).

Lidocaine concentrations were also high in the maternal brain and kidney (figs. 3, 4, and 6). Mean values were 31.9 and 42.3 μg/g at 1 minute, declining to 4.0 and 14.9 μg/g, respectively, after 25 minutes. Differences between mean lidocaine levels in the maternal brain after 2 and 5 minutes and in the kidney after 1, 2, and 5 minutes were not significant. Mean drug concentrations in the fetal brain and kidney were much lower than those in the mothers. In the brain, the mean concentration reached a maximum of 9.7 μg/g at 2 minutes, amounting to 46 per cent of the level in the mothers (fig. 6). It subsequently declined to 2.9 μg/g after 25 minutes. In the fetal kidney, mean lidocaine concentrations were proportionately even lower. The concentration had risen to 5.8 μg/g after 2 min-
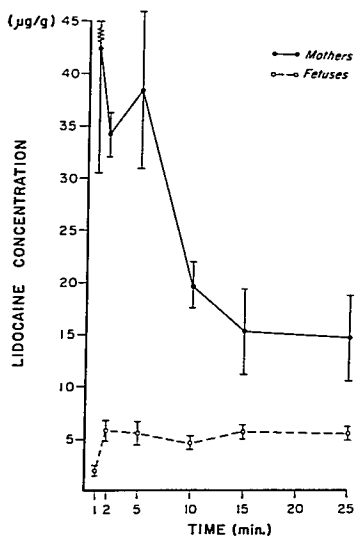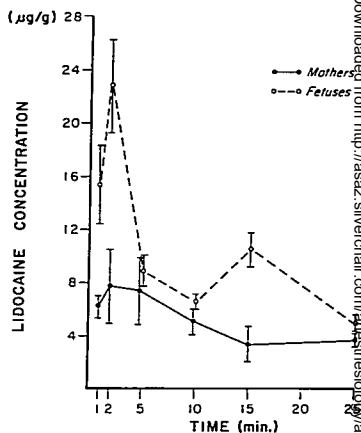

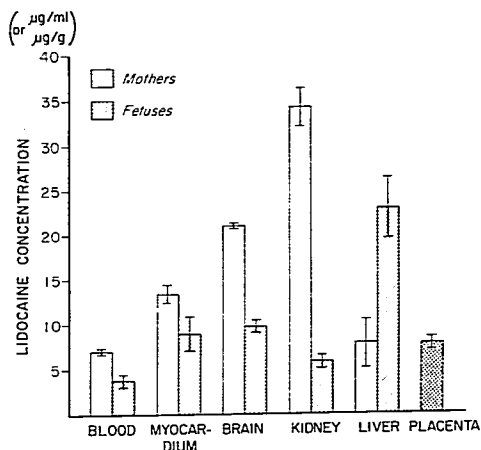Fic. 4. Mean lidocaine concentrations in the maternal and fetal kidneys.

Fig. 6. Mean lidocaine concentrations in maternal and fetal tissues 2 minutes after injection.

utes, at which time it amounted to only 17 per cent of the maternal level, and it remained almost unchanged thereafter.

The fetal liver contained significantly higher mean lidocaine concentrations than did the maternal liver after 1, 2, and 15 minutes (fig. 5). The peak value, achieved at 2 minutes, was 22.9 μg/g in the fetal liver but only 7.8 μg/g in the maternal liver (fig. 6). In the fetuses, the hepatic lidocaine levels had declined to 6.7 μg/g after 10 minutes but rose again to 10.5 μg/g after 15 minutes and finally decreased to 5.1 μg/g after 25 minutes. In the mothers, mean lidocaine concentrations declined slowly to 3.6 μg/g at 15 minutes and remained the same after 25 minutes.

Lidocaine concentrations in the placenta were generally low, not exceeding 7.7 μg/g at their maximum, at 2 minutes (fig. 6). They had fallen to 4.3 μg/g after 10 minutes and remained almost unchanged thereafter.

Discussion

Moderate fetal blood levels of lidocaine were present as early as 1–2 minutes after its administration to the mother, in accord with previous reports indicating rapid transfer of local anesthetics across the placenta.[1-4] We

and others also found a persistent gradient for lidocaine between maternal and fetal blood.[2,4] Even after 25 minutes the mean drug concentration in the fetal blood amounted to only 64 per cent of that in the maternal blood. This concentration gradient has been attributed to uneven perfusion of the placenta by maternal and fetal circulations[2] and to the difference between maternal and fetal blood in plasma binding of lidocaine.[10]

Any drug transferred across the placenta is carried to fetal tissues, where its uptake depends on the tissue/blood partition coefficient of the drug and the tissue perfusion. Our results indicate that rapid placental transfer of lidocaine is paralleled by its rapid distribution to highly perfused fetal organs, particularly the liver, heart, and brain. The liver was the only organ in which lidocaine levels in the fetus exceeded those in the mother (fig. 5). The major part of umbilical venous blood perfuses the fetal liver, and only a small fraction is shunted directly into the inferior vena cava via the ductus venosus.[11] Thus, any drug crossing the placenta is immediately brought to the fetal liver. Another reason for the high hepatic concentrations may be the well-known deficiency of drug-metabolizing enzymes in

the fetal and neonatal liver.[12] Substantial hepatic uptake of drugs transmitted across the placenta has also been demonstrated with thiopental,[13] [82]Br–halothane,[14] and ^{14}C–cyclamate.[15] The secondary increase in mean lidocaine concentration in the fetal liver after 15 minutes is unexplained.

Relatively high concentrations of lidocaine in the fetal heart could account for its susceptibility to local anesthetics administered to the mother. After 2 minutes, the mean myocardial level of lidocaine in the fetuses was not significantly different from that in the mothers (figs. 2 and 6). Since myocardial toxicity of local anesthetics is enhanced by hypoxia and acidosis,[16] drug levels well tolerated by the mother might cause severe myocardial depresson of a partly asphyxiated fetus.

Fetal kidneys contained the lowest concentrations of lidocaine (fig. 4), probably because renal blood flow in the fetus is low compared with that in the adult.[17]

Placental uptake of the drug was also limited. Similar results were obtained with [82]Br-halothane[14] and thiopental,[18] indicating that, unlike the fetal liver, the placenta plays a limited role in decreasing the drug concentration in fetal blood before it reaches vital organs such as the heart and brain.

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