Pharmacokinetics and Renal Excretion of Diphenhydramine and Its Metabolites, Diphenylmethoxyacetic Acid and Diphenhydramine-*N*-Oxide, In Developing Lambs

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ABSTRACT: The developmental disposition of diphenhydramine (DPHM) and its metabolites, diphenylmethoxyacetic acid (DPMA) and DPHM-*N*-oxide (DPHMNO), was investigated in postnatal lambs. Lambs received a DPHM intravenous (iv) bolus 15 days (Group A; $n = 5$) or 2 months (Group B; $n = 6$) after birth. Total body clearance of DPHM in postnatal lambs (Group A = 138.7 ± 80.5 mL/min/kg; Group B = 165.7 ± 51.3 mL/min/kg) was similar to the nonplacental clearance values (i.e., the component of fetal total body clearance that is not due to elimination via the placenta) estimated for fetal lamb (116.3 ± 49.6 mL/min/kg), and significantly greater than estimates in adult sheep (38.5 ± 12.3 mL/min/kg). In addition, Group A DPHM renal clearance (CL_r, >1.80 ± 1.24 mL/min/kg) was similar to that of the fetus (2.06 ± 0.24 mL/min/kg), and significantly greater than that for Group B (0.26 ± 0.17 mL/min/kg) and the adult (0.012 ± 0.005 mL/min/kg). In contrast, similar to the fetal situation, postnatal DPMA CL_r (Group A = 0.02 ± 0.02 mL/min/kg; Group B = 0.05 ± 0.01 mL/min/kg) was significantly less than adult values (0.53 ± 0.19 mL/min/kg). Because DPMA is not sequentially metabolized in sheep, the lower CL_r in postnatal lambs results in longer apparent elimination half-lives of this metabolite (Group A = 90.4 ± 32.2 h; Group B = 13.13 ± 11.0 h) compared with that in the adult (2.9 ± 1.6 h). No age-related difference in DPHMNO CL_R was observed. Alterations in the CL_r of DPHM and DPMA are likely related to differences in the rate of development of mechanisms (i.e., tubular secretion and reabsorption and glomerular filtration rate) involved in the urinary drug excretion of organic acids and bases. J Pharm Sci 89: 1362–1370, 2000

Keywords: diphenhydramine; postnatal drug disposition; renal drug excretion; sheep

INTRODUCTION

Diphenhydramine (DPHM) is a first-generation H_1-receptor antagonist. Therapeutically, it is used to relieve allergic symptoms such as hay fever, rhinitis, cough, urticaria, dermatoses, and pruritis.[1] DPHM is also commonly used for relief of motion sickness, nausea, and vomiting, and as a hypnotic.[1] Because it is often used during pregnancy, our laboratory has investigated the disposition of DPHM and its metabolites, diphenylmethoxyacetic acid (DPMA) and DPHM-*N*-oxide (DPHMNO), in the maternal–fetal unit using chronically instrumented pregnant sheep.[2–5] We also have attempted to assess fetal drug elimina-

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tion capacity for this compound.[3] Our pregnant sheep investigations involved the use of a two-compartment model that allows for the separation of placental and nonplacental components of total drug clearance from both the maternal and fetal compartments.[6] Thus, estimates of fetal nonplacental clearance (CL_{fo}) are considered to be a measure of the fetal lamb's intrinsic ability to eliminate the compound in question. In these studies, we found that maternal nonplacental clearance (CL_{mo}) contributed to ~95% of total maternal clearance.[5] In contrast, CL_{fo} accounted only for ~40% of total fetal clearance.[5] Furthermore, both weight-normalized fetal nonplacental and renal clearances of DPHM were higher compared with those of the adult. In fact, weight-normalized CL_{fo} was ~3 times that observed in the ewe (i.e., CL_{mo}) and is the highest yet found out of all the drugs previously examined in fetal lamb.[3] Another finding from these studies was that fetal DPMA renal clearance was negligible because of the limited organic acid secretion by the fetal kidney.[5]

As a continuation of these studies, we investigated the developmental disposition of DPHM in postnatal lambs. DPHM is commonly administered to children in cough, common cold, and antimotion sickness medications and its high concentration in breast milk represents a potential route of neonatal exposure.[7–9] However, detailed studies on developmental changes in DPHM disposition are lacking. The objective of this study was to examine the developmental alterations in the disposition of DPHM and its metabolites in postnatal lamb. This study also provided us with a unique opportunity to examine differences in developmental changes in the renal excretion of acidic (i.e., DPMA) and basic (i.e., DPHM) compounds.

EXPERIMENTAL SECTION

Animals and Surgical Preparation

A total of 11 Dorset–Suffolk cross-bred lambs were employed in this study. The study was approved by the University of British Columbia Animal Care Committee, and the procedures performed on sheep conformed to the guidelines of the Canadian Council on Animal Care. The 11 lambs were of two different ages: groups A ($n = 5$, ~15 days old) and B ($n = 6$, ~2 months old). Mean body weights for Group A and Group B lambs were 6.3 ± 1.5 and 12.7 ± 2.9 kg, respectively. All lambs were surgically prepared 7–8 days prior to the experiment under isoflurane (1%) anesthesia. Briefly, polyvinyl catheters (Dow Corning, Midland, MI) were implanted in a carotid artery and a jugular vein (catheter i.d. 1.02 mm and o.d. 2.16 mm). A third larger diameter catheter was implanted in the urinary bladder via an abdominal incision. The catheters were tunneled subcutaneously and exteriorized via a small incision either between the shoulder blades (carotid artery and jugular vein catheters) or on the flank of the lamb (urinary bladder catheter) and securely bandaged. All catheters were flushed daily with ~2 mL of sterile 0.9% sodium chloride containing 12 units of heparin/mL to maintain catheter patency. Ampicillin (500 mg) was administered intramuscularly on the day of the surgery and for 3 days postoperatively. Following surgery, animals were returned to holding pens with their mothers and allowed to recover for 7–8 days prior to experimentation.

Following the recovery period, the lambs were moved to monitoring pens adjacent to and in full view of their mothers. The urinary bladder catheter was allowed to drain by gravity into a sterile reservoir. While in the holding pens, lambs were fed Deluxe Lamb Milk Replacer (Canadian Nursette Distributor Ltd., Canrose AB) and had free access to hay, grain, and water.

Experimental Protocols

Group A

Group A experiments were performed at ~15 days of age (mean = 15.6 ± 1.3 days). A 10-mg intravenous (iv) DPHM bolus was administered via the jugular vein catheter over 30 s. Serial blood samples (2 mL) were collected from the carotid artery catheter at 2.5, 5, 10, 20, 30, 45, 60, 90, 120, and 180 min, and 4, 6, 9, 12, 24, 36, 48, 72, and 96 h following drug administration. Cumulative urine samples were also collected for 96 h.

Group B

Group B experiments were performed at ~2 months of age (mean = 61.3 ± 1.5 days). Group B lambs were administered a 20-mg iv DPHM bolus via the jugular vein catheter over 30 s. Serial blood samples and cumulative urine were collected as for Group A, except sampling of both blood and urine ended at 72 h following drug administration.

DPHM doses were prepared in sterile water for

injection and were sterilized by filtering through a 0.22-m nylon syringe filter (MSI, Westboro, MA) into a capped empty sterile injection vial.

All blood samples were placed into heparinized Vacutainer tubes (Becton-Dickinson, Rutherford, NJ) and centrifuged at 3000 *g* for 10 min. The plasma supernatant was removed and placed into clean borosilicate test tubes with polytetrafluoroethylene-lined cap. All collected samples were stored frozen at –20 °C until the time of analysis.

Determination of DPHM Plasma Protein Binding

DPHM unbound fraction was determined *ex vivo* in pooled plasma samples using the equilibrium dialysis procedure described by Yoo et al.[2]

Drug and Metabolite Assay

DPHM and DPHMNO concentrations in all biological fluids were measured by a liquid chromatographic tandem mass spectrometric (LC-MS/MS) analytical method previously developed in our laboratory.[4] The limit of quantitation for DPHM and DPHMNO were 0.2 and 0.4 ng/mL, respectively. DPMA concentrations in plasma and urine were measured by a previously developed gas chromatographic mass spectrometric analytical method.[10] The limit of quantitation for DPMA was 2.5 ng/mL.

Pharmacokinetic Analyses

Pharmacokinetic parameters were calculated by standard methods as described in Gibaldi and Perrier.[11] The apparent elimination half-lives ($t_{1/2}$) of DPMA and DPHMNO were estimated from their terminal elimination phases. DPHM terminal elimination half-life ($t_{1/2}$) and area under the arterial plasma concentration–time profile from zero to infinity ($AUC_{0-\infty}$) were obtained from a two-compartment model fitting of the data using nonlinear least-squares regression software, WinNonlin (Scientific Consulting, Inc., Apex, NC). All model fittings were carried out using a weighting factor of 1/predicted y^2.

Renal clearances for DPHM and DPHMNO were calculated by dividing the total amount of each compound excreted in urine by their respective plasma $AUC_{0-\infty}$. DPHMNO plasma $AUC_{0-\infty}$ was calculated by the linear trapezoidal rule. Because of the long apparent plasma $t_{1/2}$ of DPMA, the $AUC_{0-\infty}$ could not be estimated accurately. Consequently, the mean DPMA renal clearance was estimated by dividing the average urinary excretion rate of each urine collection interval by the plasma drug concentration at the time corresponding to the midpoint of the collection interval. The resulting DPMA CL_r values for all urine collection intervals were averaged to get the mean DPMA CL_r for the lamb.

Statistical Analysis

All data are reported as mean ± standard deviation (SD). Pharmacokinetic parameters were compared using an unpaired *t*-test (for two groups) or ANOVA (analysis of variance) followed by Fischer's LSD multiple comparison test (for more than two groups). The significance level was $p < 0.05$ in all cases. Linear regression analysis was performed using SigmaPlot Version 5.0 (SPSS Inc., Chicago, IL).

RESULTS

Comparative Pharmacokinetics of DPHM in Fetal, Postnatal and Adult Sheep

Figure 1 is a semilogarithmic plot of mean DPHM concentration versus time for Group A and Group B lamb plasma following iv administration. With the exception of two animals from Group A, the plasma profile for both lamb groups is best described by a biexponential equation; a rapid DPHM distribution in these two animals probably resulted in an apparent monoexponential plasma profile. Pharmacokinetic parameters for Groups A and B lambs are presented in Table 1. DPHM weight-normalized total body clearance

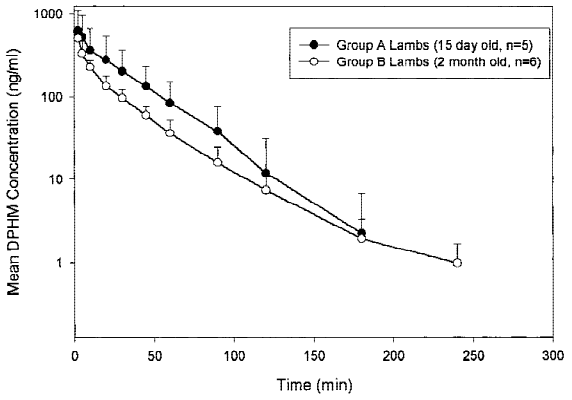

Figure 1. Mean DPHM concentration versus time profiles of DPHM in Group A and Group B lambs plasma following iv bolus administation of DPHM.

Table 1. Pharmacokinetic Parameters for Fetal, Group A, Group B, and Adult Sheep

Parameter	Age Group			
	Fetus[a]	Group A (15 day)	Group B (2 month)	Adult[a]
C_{ltb} (mL/min/kg)	116.3 ± 49.6[b]*	138.7 ± 80.5*	165.7 ± 51.3*	38.5 ± 12.3[c]**
V_{dss} (L/kg)	13.1 ± 3.1*	4.8 ± 2.9**	4.4 ± 2.4**	2.1 ± 1.1**
$t_{1/2\beta}$ (min)	33.1 ± 21.6*	27.6 ± 9.7[d]*	22.4 ± 5.1*	57.2 ± 18.2**
MRT (min)	51.3 ± 18.9**	35.4 ± 9.4*	25.5 ± 5.9*	60.8 ± 19.1**

[a] Data from Kumar et al. (1999).[5] [b]Fetal nonplacental clearance value. [c]Maternal nonplacental clearance value. [d]$t_{1/2}$ from 2 animals in group estimated using 1-compartment model; $t_{1/2}$ from remaining 3 animals estimated using 2-compartment model; Values with different numbers of asterisks (* or **) are significantly different as determined by Fischer's LSD Multiple-Comparison Test ($p < 0.05$).

(CL_{tb}) and other pharmacokinetic parameters in Table 1 were not significantly different between the two postnatal lamb groups. When compared with our previous adult and fetal estimates,[5] the mean CL_{tb} for both groups A and B were similar to fetal CL_{fo}, but significantly higher than adult CL_{mo}. No significant differences were found when comparing steady-state volume of distribution (Vd_{ss}) between the postnatal lambs and adult sheep; however; VD_{ss} was significantly larger for fetal lambs. Elimination half-life ($t_{1/2}$) and mean residence time (MRT) for DPHM in postnatal lambs were significantly shorter compared with the corresponding adult values.

Plasma unbound fractions ranged between 0.05 and 0.29 for Group A and between 0.07 and 0.26 for Group B. The mean DPHM plasma unbound fraction (f_u) for Group A (0.15 ± 0.10), Group B (0.15 ± 0.06) and adult sheep (0.12 ± 0.07)[12] were not significantly different. However, DPHM f_u for both groups of postnatal lamb and adult sheep were significantly lower than values previously observed for fetal lamb (0.30 ± 0.09).[12] Figure 2 shows a highly significant relationship between CL_{tb} and DPHM plasma unbound fraction in pooled data.

Plasma Disposition of DPHM Metabolites

A representative profile for DPMA and DPHMNO concentrations after iv administration is presented in Figure 3. As can be observed in Figure 3, DPMA elimination from plasma is extremely slow in comparison with that of DPHM and DPHMNO, especially in Group A lambs. Figure 4 compares the apparent elimination $t_{1/2}$ of DPMA in fetal, postnatal, and adult sheep. DPMA apparent elimination $t_{1/2}$ is significantly longer for Group A lambs compared with all other groups. No such differences existed for DPHMNO apparent elimination $t_{1/2}$ with age.

Urinary Excretion of DPHM, DPMA, and DPHMNO

After birth, the renal clearance (CL_r) of DPHM decreases with age. DPHM CL_r for fetal (2.06 ± 0.24 mL/min/kg, $n = 5$)[3] and Group A lambs (1.80 ± 1.24 mL/min/kg, $n = 5$) were not significantly different. However, DPHM CL_r values for both fetal and Group A lambs were significantly higher than that for Group B lambs (0.26 ± 0.17 mL/min/kg, $n = 4$; Figure 5A). The adult DPHM CL_r of 0.012 ± 0.005 mL/min/kg ($n = 4$)[3] was the lowest in comparison with all other age groups (Figure 5A). As expected from the DPHM CL_r

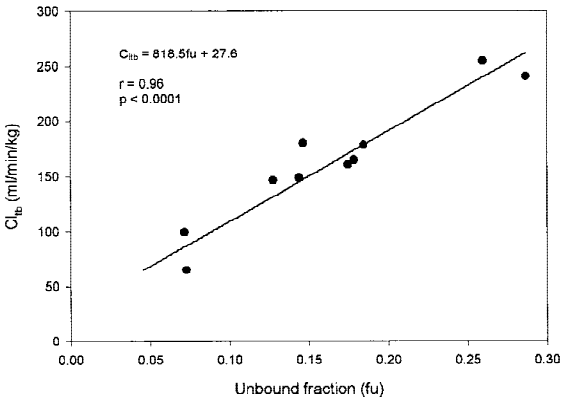

Figure 2. DPHM total body clearance versus unbound fraction for postnatal lambs (Group A and B). Regression line shows relationship between total body clearance and DPHM unbound fraction.

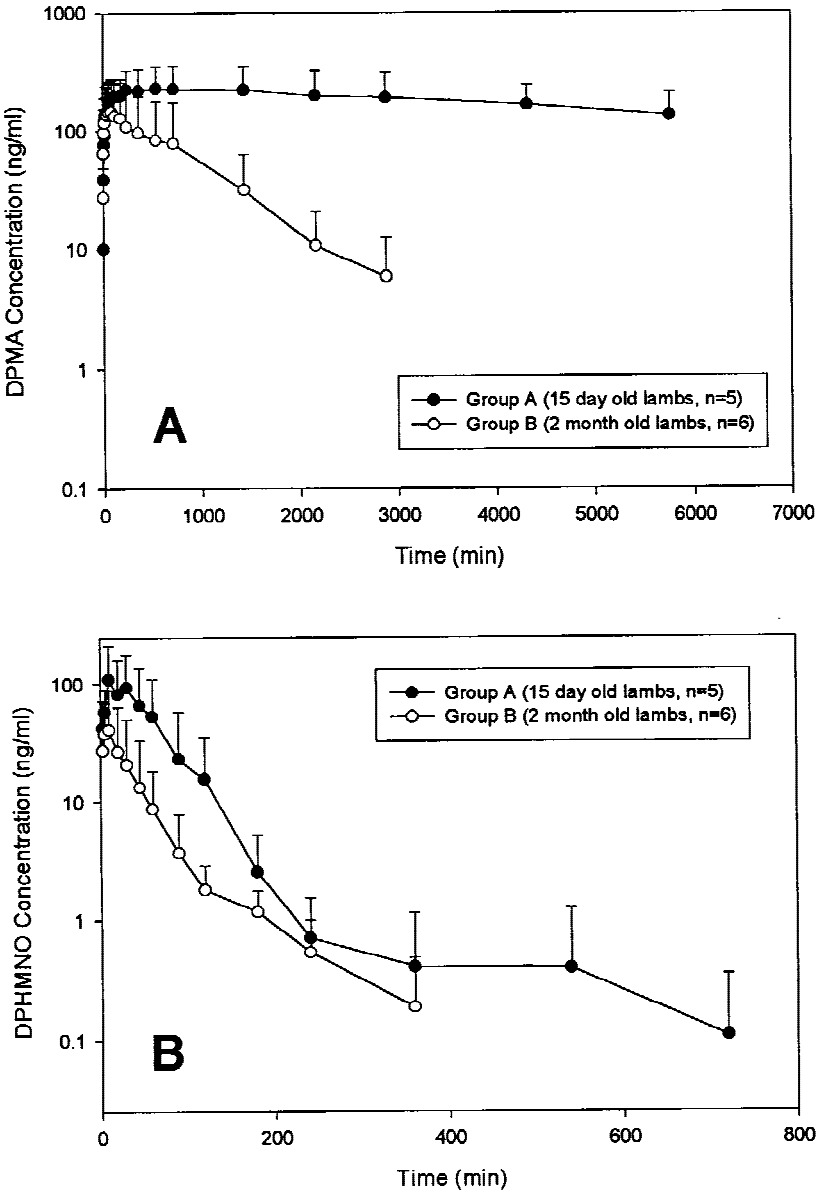

Figure 3. (A). Mean DPMA concentration versus time profiles for Group A and Group B lambs. (B). Mean DPHMNO concentration versus time profiles for Group A and Group B lambs.

data, the percentage of the dose excreted in urine as the parent compound was significantly higher for Group A (1.32 ± 0.73%, $n = 5$) in comparison with Group B lambs (0.14 ± 0.08%, n = v4).

In contrast to DPHM, DPMA CL_r increased progressively with age (Figure 5B). Mean DPMA CL_r was the lowest in the fetus (0.007 ± 0.006 mL/min/kg, $n = 3$)[5] followed by Group A (0.02 ± 0.02 mL/min/kg, $n = 5$), Group B (0.05 ± 0.01 mL/min/kg, $n = 4$), and finally adult sheep (0.53 ± 0.19 mL/min/kg, $n = 5$).[5] DPMA CL_r was significantly lower in all groups of lambs compared with adult values (Figure 5B). Mass balance data were not compared because of incomplete collection of this metabolite in lambs during the experimental period.

No significant changes in DPHMNO renal clearance were observed with age. However, a significantly higher percentage of the DPHM dose was excreted as DPHMNO in Group A lambs (2.5%) compared with the other age groups (<0.4%).

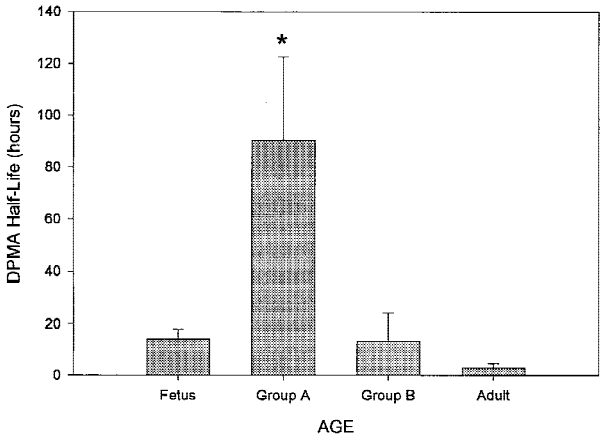

Figure 4. DPMA plasma half-life in fetal, Group A, Group B, and adult sheep. Fetal and adult data are from Kumar et al. (1999).[5] Key: (*) denotes significant difference from the fetus, Group B lambs, and adult values ($p < 0.05$).

DISCUSSION

The results of the present study indicate that DPHM CL_{tb} in postnatal lambs up to 2 months of age is similar to previously calculated fetal CL_{fo} and is ~3–4 fold higher compared with that in adult sheep. A similar situation seems to occur in humans where DPHM CL_{tb} in children was ~2-fold higher than adult values.[7] The observed DPHM CL_{tb} in Group A lambs exceeds estimated values of hepatic blood flow (~58 mL/min/kg),[13] suggesting the presence of an extrahepatic clearance component. A similar situation exists for 2-month-old lamb, where DPHM CL_{tb} approximates the total cardiac output (~160 mL/min/kg).[14] Because the lung receives the entire cardiac output, significant DPHM lung uptake (via either metabolism or strong tissue binding) in postnatal lambs would explain our observations. This explanation is a possibility because the accumulation of high concentrations of DPHM in the lung have been observed previously in rat,[15,16] guinea pig,[15] and humans.[17] DPHM volume of distribution estimates for both groups of postnatal lamb and adult sheep were not significantly different. However, postnatal lamb Vd_{ss} was significantly lower than fetal values. A decrease in Vd_{ss} following birth is expected because drug administered postnatally cannot distribute to the maternal compartment that is available to the fetus. DPHM half-life and MRT for adult sheep were ~2-fold higher than that observed for both Groups A and B. A similar situation occurs in humans, where $t_{1/2}$ in adults is ~2-fold higher than that observed in children.[7] Thus, it appears that the pharmacokinetics of DPHM in plasma does not change significantly during the first 2 months of life and, aside from expected differences in Vd_{ss}, are similar to those in the fetus.

A linear relationship was observed between CL_{tb} and unbound drug fraction for postnatal lambs from both groups. We also observed a similar close relationship[18] between plasma protein binding and clearance in adult and fetal sheep, suggesting that plasma unbound fraction is an important determinant of DPHM systemic clearance.

As part of this study, we examined the developmental disposition of the DPHM metabolites, DPMA and DPHMNO, in postnatal lambs. No age-related changes were observed in the apparent plasma elimination $t_{1/2}$ of DPHMNO. On the other hand, DPMA apparent elimination $t_{1/2}$ increased dramatically after birth and then decreased with age. Previously, we have shown that DPMA administered to the fetus is almost entirely eliminated via the placenta and excreted in maternal urine.[5] Therefore, the long apparent elimination $t_{1/2}$ after birth is expected because the main source of DPMA elimination for the fetus is via the placenta. Following this increase, DPMA $t_{1/2}$ decreases by ~30-fold by adulthood. DPMA is not sequentially metabolized in sheep and is eliminated almost entirely by renal excretion.[5] Thus, changes in DPMA apparent elimination $t_{1/2}$ after birth may be attributed to developmental changes in renal clearance of the compound, as discussed later.

Renal clearance of DPHM decreased with age after birth. Previously, we found significant differences in the ability of fetal and adult sheep to excrete DPHM.[3] DPHM CL_r in fetal lamb (~2 mL/min/kg) exceeded reported values of glomerular filtration rate (GFR; ~ mL/min/kg),[19] suggesting the involvement of tubular secretion. The ability of fetal lamb in late gestation to secrete organic cations, such as tetraethylammonium,[20] meperidine,[21] cimetidine,[22,23] and ranitidine,[23] has also been observed by others. In fact, for ranitidine and cimetidine, the processes involved in their secretion were operating at full efficiency by 80 days of gestation.[23] In contrast, DPHM CL_r in adult sheep (~0.01 mL/min/kg)[3] was substantially less than the reported GFR (~2.4 mL/min/kg).[19] This result suggests reabsorption in the proximal tubule of a portion of the DPHM load that is filtered and/or secreted. The data in the current

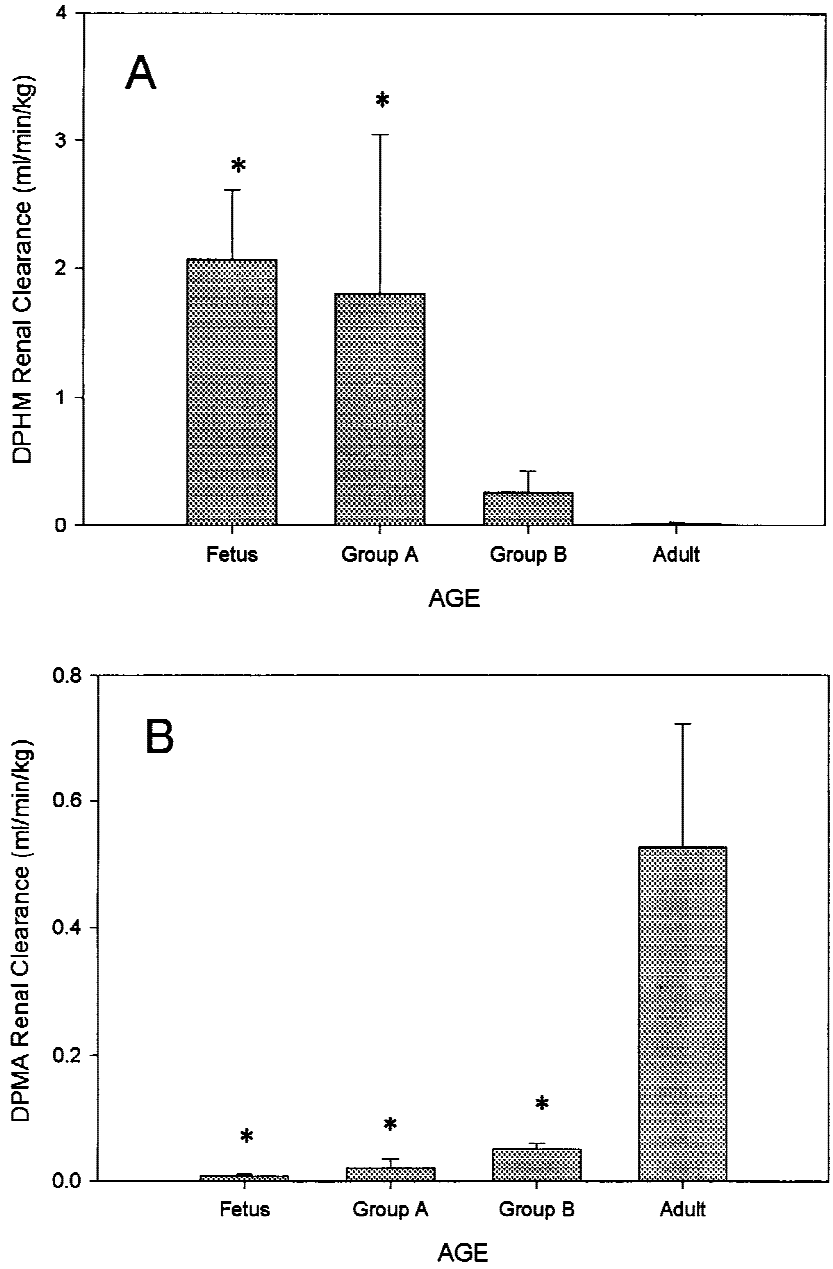

Figure 5. (A). Changes in DPHM renal clearance with age. Fetal and adult data are from Kumar et al. (1999).[5]. Key: (*) denotes significant difference from the adult value ($p < 0.05$). (B). Changes in DPMA renal clearance with age. Fetal and adult data are from Kumar et al. (1999).[5] Key: (*) denotes significant difference from the adult value ($p < 0.05$).

study indicate that significant reabsorption likely develops after the first 2 weeks of life because the DPHM CL_r values of Group A and fetal lambs are similar (Figure 5A). A similar delayed development of tubular reabsorption in comparison with other kidney processes (i.e., tubular secretion and glomerular filtration) has also been observed in human infants for various compounds.[24] This change in DPHM reabsorption may be in part attributable to age-related increases in urine pH[25] and increases in urine concentrating capacity.[26] Differences in DPHM CL_r between Group A and B lambs are reflected in the significantly higher percentage of the administered dose excreted as the unchanged drug in Group A (1.32 ± 0.73%) in comparison with Group B (0.14 ± 0.08%).

In contrast to DPHM CL_r, DPMA CL_r appeared to increase with age. The mechanisms responsible for the tubular secretion of organic acids are not fully functional in the late gestational fetal lamb.[27] Thus, the urinary secretion of acidic compounds, such as *para*-aminohippurate,[20] valproic acid,[12] and indomethacin,[28] by the fetal lamb is limited. Our data for postnatal lamb shows a slow increase in mean DPMA CL_r during the first 2 months of life (Figure 5B). Increases in organic acid excretion capacity with age are mainly attributable to increases in intrinsic renal tubular transport capacity.[27] In addition, age-related increases in renal blood flow and GFR may also play a role.[27] As already mentioned, the dramatic decreases in DPMA apparent elimination $t_{1/2}$ observed postnatally reflect the changes in DPMA CL_r because the elimination of DPMA in sheep is almost entirely via renal excretion.

No significant differences were detectable in the CL_r of DPHMNO among different age groups. The higher percentage of the dose excreted as DPHMNO in Group A lambs suggests that either a larger fraction of the dose is metabolized via the *N*-oxidation pathway and/or there is reduced sequential clearance of this metabolite. However, the urinary excretion of DPHMNO appears to be of minor significance to overall DPHM elimination in sheep in spite of this observed difference.

In summary, DPHM CL_{tb} in lambs at 15 day and 2 months of age is much higher than in adult sheep, and is similar to fetal CL_{fo} estimates. Thus, the decrease in DPHM CL_{tb} to adult values likely occurs after the first 2 months of life. The age-related alterations in renal clearance of the basic compound, DPHM, and its carboxylic acid metabolite, DPMA, appear to follow opposite trends (i.e., DPHM CL_r decreases and DPMA CL_r increases with age). The opposing trends are likely related to differences in the rate of development of kidney mechanisms (i.e., tubular secretion of organic acids and bases, tubular reabsorption, and GFR) involved in drug excretion.

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ABBREVIATIONS

$AUC_{0-\infty}$	Area under the arterial plasma concentration-time profile from zero to infinity
CL_{mo}	Maternal non-placental clearance of the total drug
Cl_{fo}	Fetal non-placental clearance of the toal drug
Cl_r	Renal clearance
Cl_{tb}	Total body clearance of the total drug
DPHM	Diphenhydramine
DPHMNO	Diphenhydramine N-oxide
DPMA	Diphenylmethoxyacetic acid
fu	unbound fraction
GFR	glomerular filtration rate
KCl	Potassium chloride
MRT	Mean residence time
NADPH	Reduced β-nicotinamide-adenine dinucleotide tetrasodium salt
SD	Standard deviation
Tris	Tris(hydroxymethyl) aminomethane
$t_{1/2\beta}$	terminal elimination halflife
$t_{1/2}$	half-life

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