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LIVER VOLUME AS A DETERMINANT OF DRUG CLEARANCE IN CHILDREN AND ADOLESCENTS

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ABSTRACT:

Many drugs eliminated by the liver exhibit age-related differences in systemic clearance, necessitating different dosage requirements in children and adults. However, the physiological basis for these age-related changes is not well defined, including the importance of liver size in determining systemic clearance. Therefore, magnetic resonance imaging was used to determine liver volume in pediatric and adolescent patients, in whom systemic clearance of three model substrates [lorazepam (0.03 mg/kg), antipyrine (10 mg/kg), and indocyanine green (ICG; 0.5 mg/kg)] was also determined. In 16 children (ages 3.3–18.8 years; 8 boys), liver volume ranged from 469 to 1640 ml (median 973), and was significantly related to age, body weight, and body surface area (BSA). Younger children had larger livers normalized to body weight (ml/

kg), but there was no difference when liver volume was normalized to BSA (ml/m²). Unnormalized lorazepam and ICG clearances (ml/min) were significantly related to absolute liver volume ($r^2 = 50.2\%$ and 31.4%, respectively), whereas unnormalized antipyrine clearance was not. Lorazepam, ICG, and antipyrine clearance normalized to BSA did not exhibit age-related changes, nor did lorazepam or ICG clearance normalized to body weight. However, antipyrine clearance normalized to body weight decreased significantly with increasing age ($r^2 = 36.9\%$, $p = 0.012$), as did antipyrine clearance relative to liver volume. Thus, age-related changes in drug clearance and the importance of liver volume may differ based on the principal hepatic mechanisms involved in drug elimination.

Hepatic biotransformation is an important route of drug metabolism and elimination, potentially influencing the efficacy and toxicity of many medications. We have previously demonstrated that the administration of three model substrates (lorazepam, antipyrine, and ICG¹) is safe and that their plasma clearances can be accurately assessed in children during a 24-hr period (1). Lorazepam is primarily eliminated by glucuronidation, antipyrine by cytochrome P450 oxidative metabolism, and ICG by biliary secretion with its clearance generally considered to be hepatic blood flow-limited. Our previous studies demonstrated that the systemic clearance of both antipyrine and ICG is greater in young children when clearance is normalized to body weight (ml/min/kg), whereas there is no significant correlation between age and clearance normalized to BSA (ml/min/m²) for any of the three model substrates (2, 3).

It has been previously suggested that functional hepatic parenchymal mass, which in normal subjects approximates liver volume, contributes to variations in the clearance of drugs, including model substrates, such as ICG (4). There is evidence that liver volume, as determined by ultrasound scans, is greater in children than adults, when expressed as a percentage of body weight. Liver volume averaged 30–35 ml/kg in two pediatric studies (5, 6), compared with

19.5–22 ml/kg in two adult studies (5, 7). When published liver volume/body weight (ml/kg) data for children and adults are combined, a decrease in the ratio is seen with increasing age (2). Age-related changes in liver volume are consistent with previous data from our institution (2, 3), which demonstrated age-related differences in ICG and antipyrine clearance normalized to body weight (ml/min/kg), but not when clearance is normalized to BSA (ml/min/m²) (2, 3). In contrast, lorazepam total clearance and unbound clearance normalized to body weight were not significantly different between children and adults (3). Although these studies identified significant differences between children and adults in the disposition of these three model substrates, they did not evaluate liver volume as a potential determinant of drug clearance.

Although ultrasound methods are adequate to differentiate adult liver volumes from those of children, ultrasound estimation of liver volume has major limitations in children and is insufficiently precise to discriminate reliably among children of different ages. Therefore, published studies estimating liver volume by ultrasound in children must be interpreted with caution. In contrast, MRI techniques to estimate liver volume are reported to be reproducible and accurate in children (8, 9), and thus offer an improved method for investigating the relationship between liver volume and hepatic drug clearance in pediatric patients.

The current study was undertaken with two primary objectives: 1) to evaluate the relationship between liver volume and patient characteristics (*i.e.* weight, BSA, and age), and 2) to evaluate the relationship between liver volume and the clearance of three model substrates—lorazepam, antipyrine, and ICG. A relationship between liver volume, as an estimate of total hepatic parenchymal mass, and systemic clearance of selected model substrates, could offer new insights into

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¹ Abbreviations used are: ICG, indocyanine green; BSA, body surface area; MRI, magnetic resonance imaging.

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TABLE 1

MRI parameters

Orientation	Slice Thickness/Gap	Measured Volume		Error
		mm	mL	
Sagittal	8/2	593	3.1	
Coronal	8/2	572	0.5	
Transverse	8/2	580	0.9	
Coronal	6/1.5	572	0.5	
Transverse	8/4	590	2.6	

the physiological basis for establishing pediatric doses based on either body weight or BSA.

Materials and Methods

Subjects. Children enrolled on one of our hepatic drug clearance protocols (for either leukemia or solid tumor patients) were eligible for this study. Patients were prospectively enrolled on this protocol to permit MRI examinations in conjunction with the previously scheduled hepatic drug clearance study. All patients were outpatients at the time of the study. The study protocol was approved by St. Jude Children's Research Hospital Institutional Review Board, and voluntary informed consent was obtained from each patient, parent, or guardian as appropriate.

Liver Volume. Liver volume estimates were determined by T1-weighted MRI and limited to the hepatic area, which did not require the use of contrast agent. The volume analysis used radiologist-selected regions of liver for each slice and a linear interpolation of the slice gap. The accuracy and reliability of the approach were verified using an anatomical liver model suspended in a Gd-doped water solution. T1-weighted imaging of the phantom was performed in three orthogonal planes (slice thickness = 8 mm, slice gap = 2 mm). The actual volume of the phantom was 575 mL, as determined by water displacement. Additional imaging was performed in the coronal (slice thickness = 6 mm, slice gap = 1.5 mm) and transverse (slice thickness = 8 mm, slice gap = 4 mm) planes. The results of this pilot study are shown in table 1. Transverse plane imaging was the preferred plane of orientation, maximizing the spatial resolution. In two patients, data obtained in the transverse plane had artifacts caused by respiratory motion, and coronal imaging was thus performed. As noted in table 1, there was no effect of the plane of orientation on the measured volume. The slice thicknesses/gaps were 14/0 mm ($N = 1$), 12/0 mm ($N = 2$), 10/0 mm ($N = 8$), 8/0 mm ($N = 2$), 8/2 mm ($N = 1$), 7/0 mm ($N = 1$), and 5/1 mm ($N = 1$).

This method was further validated by performing liver volume estimates using commercially available software provided with the imager. In this method, regions of interest delineating the periphery of the liver are drawn and volumes were automatically calculated for each slice. The volumes from the region of interest in each slice are added to estimate the total liver volume. The method used for the data reported herein was more rigorous, and was further prospectively validated by performing volume estimates using an anatomical liver model as previously described. There was excellent agreement between the two methods ($r^2 = 95\%$).

Model Substrates. Lorazepam (Ativan, Wyeth Laboratories), ICG (Cardio-Green, Hynson, Westcott & Dunning), and antipyrine were administered simultaneously as a mixture given as an intravenous infusion over exactly 5 min. Sterile antipyrine for injection was prepared in the Parenteral Medications Laboratory in the Department of Pharmaceutics at the University of Tennessee, Memphis, as described previously (7). The dosages of each compound were: lorazepam, 0.03 mg/kg, up to 1 mg maximum; ICG, 0.5 mg/kg; and antipyrine, 10 mg/kg.

Study Design. All studies were begun at 8:00 a.m. to minimize any effect of diurnal variability on hepatic blood flow or other factors involved in the hepatic clearance of these model substrates. The model substrates were administered via an indwelling intravenous catheter in one forearm, and all venous blood sampling was performed via the same catheter after liberal flushing with saline solution. Venous blood samples were collected 2, 5, 7, 10, and 12 min and at 1, 1.25, 6, 23.75, and 24 hr after infusion, as previously reported (7). Samples were placed on ice until centrifuged, and then plasma was frozen at -20°C until assayed.

TABLE 2

Patient characteristics

	Median	Range
Gender	8 boys/8 girls	
Age (yr)	9.7	3.3–18.8
Weight (kg)	40.8	11.9–88.5
BSA (m ²)	1.37	0.57–2.0
Liver volume (ml)	973.0	469–1640
Lactate dehydrogenase (IU/liter)	234.0	123.0–493.0
Alkaline phosphatase (IU/liter)	412.0	33–883.0
Albumin (g/dl)	4.2	3.3–4.9
AST (IU/liter)	36.0	22.0–121
ALT (IU/liter)	26.0	7.0–252.0
Total bilirubin (mg/dl)	0.35	0.2–0.7
Prothrombin time	11.2	10.4–20.9
Serum creatinine (mg/dl)	0.7	0.4–1.3

Liver volume was estimated on the same day the model substrates were administered or else the next clinic visit. There was never more than a 5% change in age between model substrate administration and liver volume determination.

Assay. Quantitative assays of lorazepam and antipyrine in plasma were performed by an HPLC method developed in our laboratory, as described previously in detail (10). Plasma samples were extracted in a single organic extraction procedure, and a gradient separation was achieved using a mobile phase of acetonitrile in 0.1% sodium phosphate (pH 3) and a Waters phenyl- μ BondaPak analytic column heated to 40°C (Waters Associates, Milford, MA). Phenacetin and flunitrazepam were used as internal standards for antipyrine and lorazepam, respectively, and the peaks of interest were detected by ultraviolet absorbance at 229 nm. ICG was assayed spectrophotometrically (11) at 800 nm within 2 weeks of sample collection.

Data Analysis. Lorazepam and antipyrine plasma concentrations were measured at 2 and 12 min and at 1, 1.25, 6, 23.75, and 24 hr after the end of the infusion. A biexponential function corresponding to a first-order, two-compartment model with elimination from the central compartment and a single intravenous infusion into the central compartment was fit to the serial lorazepam and antipyrine data for each subject. Primary pharmacokinetic parameters were estimated using a Bayesian algorithm as implemented in the ADAPT II software (Biomedical Simulation Resource, University of Southern California, Los Angeles, CA) (12), with prior parameter distributions from previous studies at this institution (6). Each observation was weighted by the inverse of the variance for the model prediction.

ICG plasma concentrations were measured at 2, 5, 7, 10, and 12 min. A first-order, one-compartment model was fit to the plasma ICG concentrations for each subject, using weighted nonlinear least squares regression as implemented in the ADAPT II software, with weighting by the inverse of the (constant) variance of the measured concentrations. Statistical comparisons were performed with the Wilcoxon signed-rank test, two-sample *t* test, and the Pearson correlation coefficient. Total body weight was used for parameter normalization. BSA was calculated using the Gehan-George equation (13).

Results

Patients. Sixteen children were enrolled on this study (12 with acute lymphocytic leukemia, 3 with neuroblastoma, and 1 with rhabdomyosarcoma). The demographics for these 16 children are listed in table 2. All children were in clinical remission at the time of the hepatic drug clearance and liver volume studies. Liver volume, ICG, and antipyrine clearances were determined for all 16 children. Lorazepam clearances were determined for 15 children; there was inadequate volume of plasma samples for analysis of lorazepam in the other child. Liver volume and model substrate clearances were determined within 1 day for 9 children (ages 3.3–18.8 years); within 1 month for 2 children (ages 3.3 and 7.9 years); within 3 months for 2 children (ages 15.0 and 15.9 years); within 4 months for 2 children (ages 8.4 and 13.0 years), and within 6 months for 1 child (age 15.9 years).

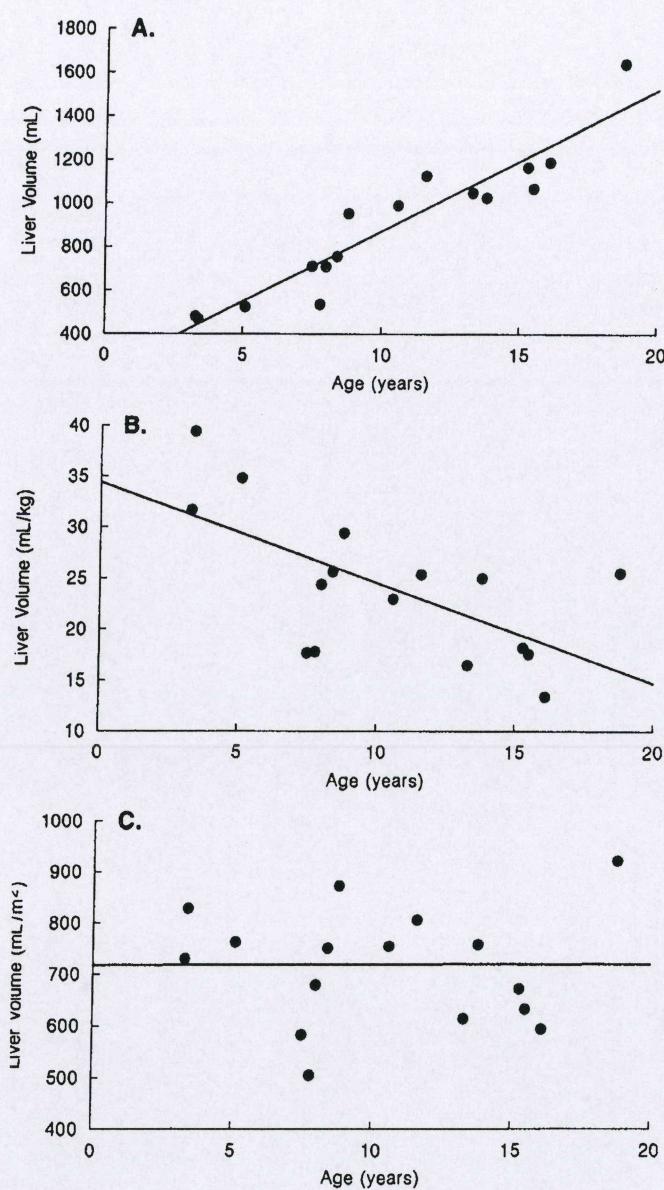


FIG. 1. Relation between age and absolute liver volume (A), liver volume normalized to body weight (B), and liver volume normalized to BSA (C).

The regression relations in (A) and (B) are statistically significant ($r^2 = 88.4\%$, $p < 0.0005$; $r^2 = 41.3\%$, $p = 0.007$; respectively). The relation in (C) is not significant.

Liver Volume Studies. Liver volumes varied over a 3.5-fold range; the median liver volume was 973 ml and ranged from 469 to 1640 ml. Liver volume was significantly related to age ($r^2 = 88.4\%$, $p < 0.0005$; fig. 1A), body weight ($r^2 = 68.2\%$, $p < 0.001$), height ($r^2 = 79.7\%$, $p < 0.001$), and BSA ($r^2 = 75.9\%$, $p < 0.001$). Liver volume normalized to body weight (ml/kg) decreased with increasing age ($r^2 = 41.3\%$, $p = 0.007$; fig. 1B). However, when liver volume was normalized to BSA (ml/m²), there was no significant change with increasing age ($r^2 = 0.0\%$, $p = 0.983$; fig. 1C).

Model Substrate Studies. Clearances of the three model substrates are summarized in table 3. Lorazepam clearance varied over a 9-fold range; the median clearance was 28.7 ml/min/m² and ranged from 8.6 to 73.4 ml/min/m². Unnormalized lorazepam clearance (ml/min) was significantly correlated with absolute liver volume ($r^2 = 50.2\%$, $p =$

TABLE 3

Clearances of model substrates

	Mean (SD)	Median	Range
Antipyrine			
ml/min	21.5 (12.1)	19.1	9.0–50.2
ml/min/m ²	18.3 (10.3)	16.7	6.9–46.1
ml/min/kg	0.63 (0.40)	0.49	0.19–1.55
ICG			
ml/min	317.4 (244.4)	266.9	57.7–880.1
ml/min/m ²	252.2 (164.8)	261.2	47.1–497.2
ml/min/kg	8.3 (5.2)	9.9	1.1–17.1
Lorazepam			
ml/min	38.6 (22.4)	39.3	8.8–83.3
ml/min/m ²	30.1 (16.6)	28.7	8.6–73.4
ml/min/kg	1.01 (0.72)	0.90	0.30–3.34

0.003; fig. 2A), BSA ($p = 0.011$), body weight ($p = 0.009$), height ($p = 0.029$), and age ($p = 0.012$). Unnormalized lorazepam clearance decreased with increases in alkaline phosphatase ($r^2 = 31.1\%$, $p = 0.038$). No other clinical characteristic was related to either unnormalized lorazepam clearance (ml/min) or clearance normalized to body size (ml/min/m² or ml/min/kg; fig. 2, B and C).

Antipyrine clearance varied over a 6.7-fold range; the median clearance was 16.7 ml/min/m² and ranged from 6.9 to 46.1 ml/min/m². Unnormalized antipyrine clearance (ml/min) was not significantly correlated with liver volume (fig. 3A). Antipyrine clearance normalized to BSA (ml/min/m²) was also significantly related to total bilirubin ($r^2 = 36.9\%$, $p = 0.012$). Antipyrine clearance normalized to BSA (ml/min/m²) was also significantly related to total bilirubin ($r^2 = 31.2\%$, $p = 0.023$), even though all serum bilirubin values were within the normal range (0.2–0.7 mg/dl) and did not exhibit a significant change with increasing age (fig. 3C).

ICG clearance varied over a 10-fold range; the median clearance was 261 ml/min/m² and ranged from 47 to 497 ml/min/m². Unnormalized ICG clearance was significantly correlated with liver volume ($r^2 = 31.4\%$, $p = 0.024$; fig. 4A), whereas neither unnormalized ICG clearance (ml/min) nor ICG clearance normalized to body size (either body weight or BSA) was significantly related to other patient characteristics evaluated (e.g. age; fig. 4, B and C).

Discussion

The present study demonstrates a ~5-fold range in liver volume among children and adolescents (ages 3.3–18.8 years) and clearly establishes that absolute liver volume increases with increasing age (and overall body size) over this age range. Liver volume in proportion to body weight (ml/kg) was smaller in older subjects (fig. 1B), a finding that is consistent with earlier studies that used ultrasonography to estimate liver volume in children and adults (5–7). In the present study, MRI technology proved to be a feasible technique to estimate liver volume noninvasively in children and adolescents, and offers theoretical advantages over ultrasound to determine liver volume in this age group. For example, ultrasound liver volume assessment is performed by measuring single lengths in three orthogonal planes, even though the liver is an irregular convoluted structure with multiple-contoured surfaces. MRI, however, calculates liver volumes as the area in contiguous planes calculated by tracing the perimeter of the liver. Ultrasound may also be limited in evaluating livers that lie in the thoracic cage, wherein ultrasound cannot penetrate through bony rib tissue. Both deep and superficial structures visualize well on magnetic resonance cross-sectional images.

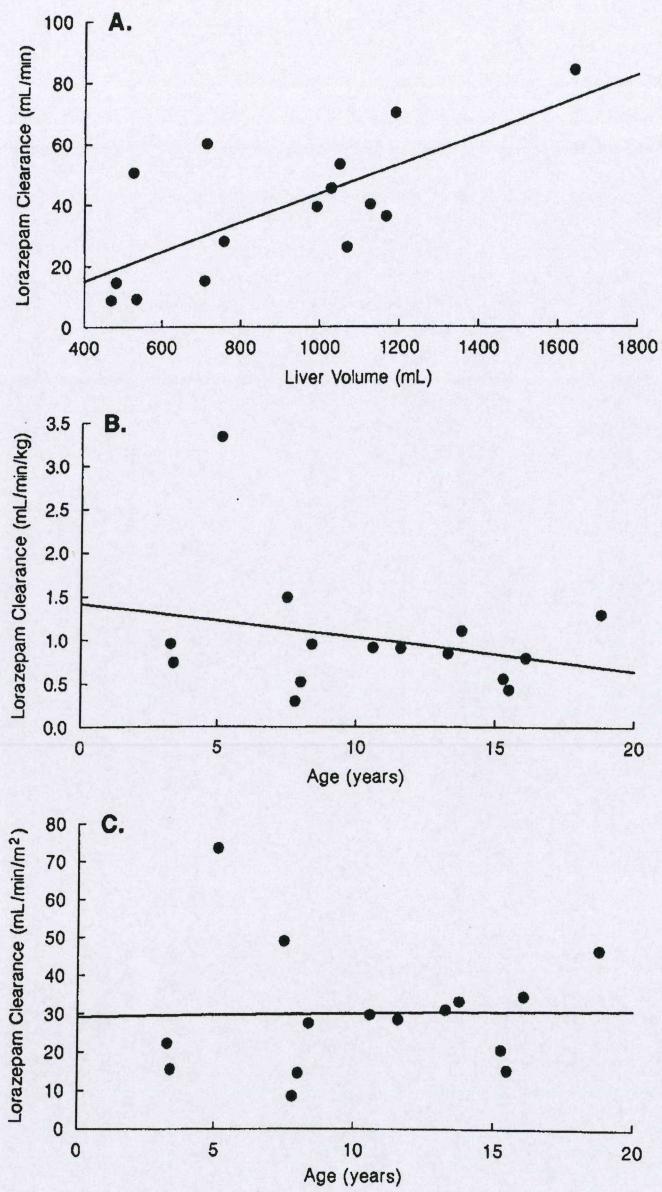


FIG. 2. Relation between lorazepam clearance and liver volume (A) and age [(B) and (C)].

In (A), the relation between unnormalized lorazepam clearance and liver volume is statistically significant ($r^2 = 50.2\%$, $p = 0.003$). (B) Relation between patient age and lorazepam clearance normalized to body weight. (C) Relation between age and clearance normalized to BSA; neither relation is statistically significant.

We have compared our current results of liver volume to standard tables of liver weight vs. age used by anatomic pathology (14, 15) and found comparable results. Liver weight increases linearly with age from 3 to 19 years, and the regression equation we calculated for age vs. liver weight from these pathology tables of normal organ weights is very similar to that derived from our data for age vs. liver volume [Liver weight (g) = $184 + 1.32 \cdot \text{Age (weeks)}$; Liver volume (ml) = $224 + 1.24 \cdot \text{Age (weeks)}$]. In addition, a report published after the submission of our study (16) reveals data for liver weight and liver volume (obtained by computed tomography), with results virtually identical to those in our study. In this report, Urata and coworkers developed a formula to calculate the standard liver volume based on

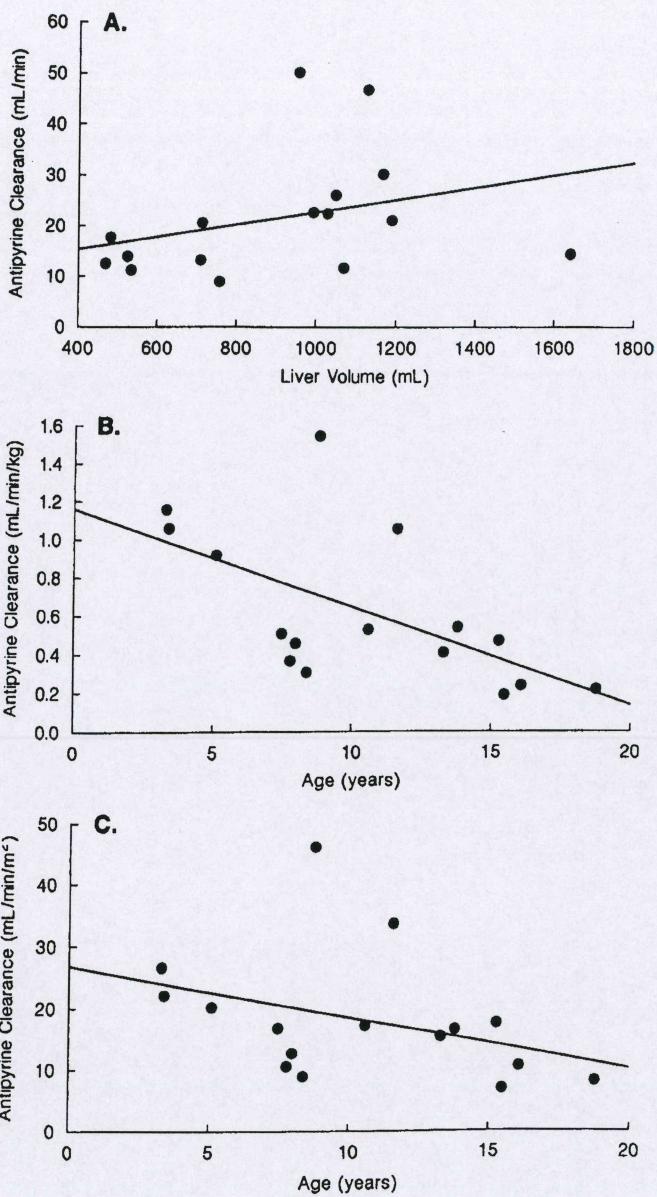


FIG. 3. Relation between antipyrine clearance and liver volume (A) and age [(B) and (C)].

In (A), the relation between unnormalized antipyrine clearance and liver volume is not statistically significant. (B) Relation between age and antipyrine clearance normalized to body weight. (C) Relation between age and clearance normalized to BSA. Relation in (B) is statistically significant ($r^2 = 35.9\%$, $p = 0.014$), whereas relation in (C) is not statistically significant.

body size and to establish the optimal graft size for use in liver transplants. Based on computed tomography, estimates of liver volume in 65 pediatric and 31 adolescent or adult patients with normal liver function, these authors report a linear decrease in liver volume, normalized to body weight (mL/kg), with increasing age, up to ~15 years of age. However, these workers found a linear relationship between liver volume and BSA over the entire age range, and the regression relationship was highly predictive ($r^2 = 96.2\%$). These authors conclude that this regression equation should provide the best estimate of optimal liver size for pediatric hepatic transplants. These conclusions are virtually identical to our findings, which demonstrated

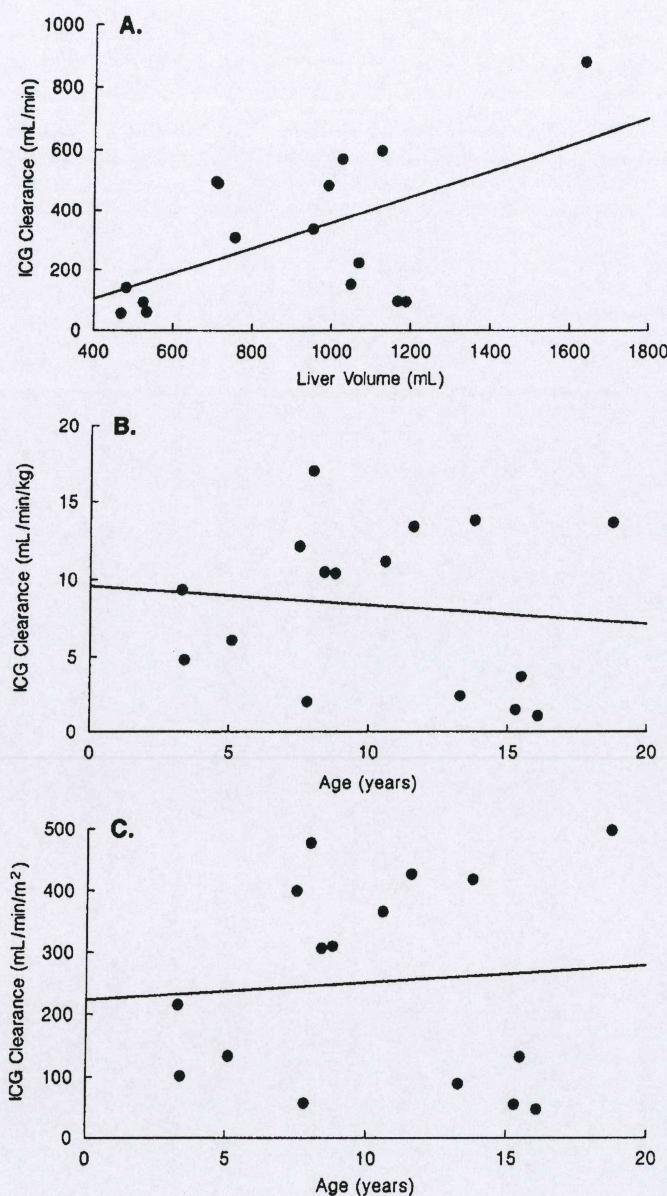


FIG. 4. Relation between ICG clearance and liver volume (A) and age (B) and (C).

In (A), the relation between unnormalized ICG clearance and liver volume is statistically significant ($r^2 = 31.4\%, p = 0.024$). (B) Relation between age and ICG clearance normalized to body weight. (C) Relation between age and clearance normalized to BSA. Neither relation is significant.

that liver volume normalized to BSA (ml/m²) was constant over the age range studied (fig. 1C).

The relatively greater liver volume (normalized to body weight) in children is consistent with faster clearances and higher pediatric dosage requirements (mg/kg) for many drugs eliminated primarily by hepatic mechanisms (17, 18). The assessment of the plasma clearances of three model substrates (lorazepam, antipyrine, and ICG) during a 24-hr period has been shown to be feasible and safe (7, 19, 20). Lorazepam is primarily eliminated by glucuronidation and ICG by biliary secretion, with its clearance generally considered to be hepatic blood flow-limited. Antipyrine is metabolized to three major metabolites by several cytochrome P450 enzymes, which have recently been identified (21, 22). These studies indicate that conversion to the 4-hydroxy metabolite is catalyzed primarily to CYP3A4 and

CYP1A2, with some minor contribution by CYP2B6. Metabolism of antipyrine to norantipyrine is catalyzed primarily by CYP2C8, CYP2C9, and CYP2C18, with some conversion by CYP1A2. The 3-hydroxymethyl metabolite is formed by CYP2C9 and CYP1A2. It is apparent that each metabolite can be formed by at least two or more cytochrome P450 enzymes, and that several of these enzymes, particularly CYP1A2, are involved in the formation of more than one metabolite. Despite the lack of specificity of antipyrine as a substrate for a specific cytochrome P450, it is widely used as a general assessment of cytochrome P450-mediated drug oxidation in humans. Thus, characterization of the clearance of these three model substrates and their relationship with liver volume provides insight into age-related differences in major processes contributing to hepatic drug elimination. Moreover, clearance of these three model substrates may more accurately reflect functional hepatic metabolic capacity (19, 23) than plasma concentrations of hepatic enzymes routinely measured as "liver function tests" (i.e. ALT, AST, and alkaline phosphatase). Plasma concentrations of these enzymes are indications of acute hepatic damage, but are neither sensitive nor precise predictors of hepatic drug-metabolizing ability.

Lorazepam, antipyrine, and ICG clearances were highly variable among the children and adolescents comprising this study population. As we have reported previously (19), hepatic drug clearance increases in some patients after they receive remission induction therapy for acute lymphocytic leukemia. This is presumably caused by eradication of leukemic infiltration in the liver that interferes with hepatic drug metabolism. Therefore, we assumed that the hepatic drug clearance estimates obtained in the present study represent baseline, or "normal" hepatic drug clearance, because all patients were in complete remission. Unnormalized clearances (ml/min) of lorazepam and ICG were significantly related to absolute liver volume ($r^2 = 50.2\%$ and 31.4%, respectively), whereas unnormalized clearance of antipyrine did not correlate with absolute liver volume. This finding suggests that the mechanisms responsible for hepatic clearance of these three model substrates differ in their relation to liver volume among children and adolescents. Liver blood flow is known to change in proportion to increasing liver volume (24), which would be expected to yield greater clearance of flow-limited substrates such as ICG. It is also conceivable that drug conjugation and biliary secretion increase in proportion to liver volume, independent of age, which may explain the greater clearance of ICG and lorazepam in proportion to increasing liver volume.

The lack of relationship between antipyrine clearance (ml/min) and absolute liver volume over this age range suggests that the overall rate of antipyrine metabolism is determined less by total liver size than by other factors known to regulate the functional expression of hepatic enzymes (e.g. age) (25). In this regard, antipyrine clearance normalized to body weight (ml/min/kg) was significantly greater in younger patients and decreased with increasing age (fig. 3B). Although there was a 200% increase in liver volume (600–1200 ml) from age 5 to 15 years, there was only a 25–30% increase in antipyrine clearance (15–20 ml/min), consistent with greater relative metabolic capacity for antipyrine in the livers of younger patients. Furthermore, antipyrine clearance normalized to liver volume was greater (30.0 vs. 15.9 ml/min/liter liver volume; $p = 0.05$) in children < 5 years ($N = 3$) vs. > 15 years ($N = 4$), as shown in fig. 5. These data suggest greater overall catalytic activity of the hepatic enzymes metabolizing antipyrine in younger children, compared with adolescents (in proportion to total hepatic parenchymal mass). Our findings are consistent with previous reports (26, 27) that some drug-metabolizing enzymes are under developmental regulation and exhibit age-related differences in

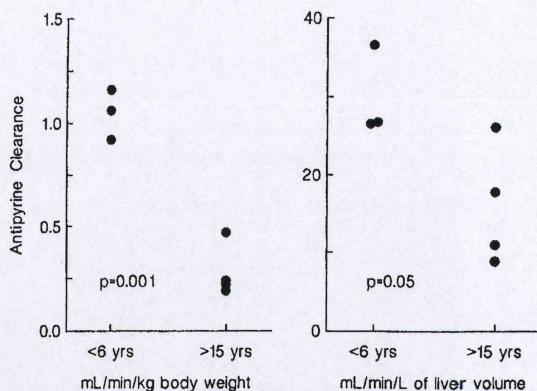


FIG. 5. Antipyrine clearance normalized to body weight and liver volume, for children <6 years old and adolescents >15 years old.

Antipyrine clearance is significantly faster in children <6, compared with adolescents >15 years of age, both when normalized to body weight (left) and liver volume (right).

their functional expression among children and adolescents. It is logical that both liver size and functional expression of specific enzymes can be important determinants of the overall hepatic metabolism of xenobiotics. In this regard, it was recently shown that the *in vitro* intrinsic clearance (V_{max}/K_m) of midazolam to 1'-hydroxymidazolam in human liver microsomes, scaled to total liver mass, accurately predicted *in vivo* systemic clearance of midazolam (28). Thus, if functional expression remains constant, a larger liver volume relative to body size could translate to greater drug clearance, normalized to body size. Moreover, when both functional expression and liver size are greater in proportion to body size, more pronounced age-related differences would be anticipated. In the present study, the latter pertained for antipyrine, for which both drug clearance relative to liver volume and liver volume relative to body weight were greater in younger children.

To the extent that antipyrine, lorazepam, and ICG are indicative of drug clearance by oxidative metabolism, conjugation and biliary secretion/liver blood flow, the present study indicates that age-related changes in drug clearance differ, based on the mechanism of hepatic elimination. These results provide further evidence that drug dosages based on total body weight will not uniformly produce similar plasma concentrations in children. Across the age range evaluated in the present study, the clearances for all three substrates, as well as liver volume, were more consistent when normalized to BSA. Thus, these data provide a potential physiological basis for the utility of BSA in determining pediatric dosages of drugs eliminated via the liver. However, there was variability in drug clearance normalized to either body weight or BSA, indicating that individualized dosing will continue to be advantageous for selected drugs with narrow therapeutic indices.

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References

- W. R. Crom, S. L. Webster, L. Bobo, M. E. Teresi, M. V. Relling, and W. E. Evans: Simultaneous administration of multiple model substrates to assess hepatic drug clearance. *Clin. Pharmacol. Ther.* **41**, 645–650 (1987).
- W. E. Evans, M. V. Relling, S. de Graaf, J. H. Rodman, J. A. Pieper, M. L. Christensen, and W. R. Crom: Hepatic drug clearance in children: studies with indocyanine green as a model substrate. *J. Pharm. Sci.* **78**, 452–456 (1989).
- W. R. Crom, M. V. Relling, M. L. Christensen, G. K. Rivera, and W. E. Evans: Age-related differences in hepatic drug clearance in children: studies with lorazepam and antipyrine. *Clin. Pharmacol. Ther.* **50**, 132–140 (1991).
- R. A. Branch, J. A. James, and A. E. Read: Major determinants of drug disposition in chronic liver disease: a study with indocyanine green and antipyrine [proceedings]. *Br. J. Clin. Pharmacol.* **2**, 370P–371P (1975).
- J. J. Grygiel, H. Ward, M. Ogborne, A. Goldin, and D. J. Birkett: Relationships between plasma theophylline clearance, liver volume and body weight in children and adults. *Eur. J. Clin. Pharmacol.* **24**, 529–532 (1983).
- G. W. Rylance, T. A. Moreland, M. D. Cowan, and D. C. Clark: Liver volume estimation using ultrasound scanning. *Arch. Dis. Child.* **57**, 283–286 (1982).
- C. J. C. Roberts, L. Jackson, M. Halliwell, and R. A. Branch: The relationship between liver volume, antipyrine clearance and indocyanine green clearance before and after phenobarbitone administration in man. *Br. J. Clin. Pharmacol.* **3**, 907–913 (1976).
- C. A. Riley and W. E. Evans: Simultaneous analysis of antipyrine and lorazepam by high performance liquid chromatography. *J. Chromatogr.* **382**, 199–205 (1986).
- G. R. McNeal, W. H. Maynard, R. A. Branch, T. A. Powers, P. A. Arns, K. Gunter, J. M. Fitzpatrick, and C. L. Partain: Liver volume measurements and three-dimensional display from MR images. *Radiology* **169**, 851–854 (1988).
- M. D. Cockman, D. A. Hayes, and B. R. Kuzmak: Motion suppression improves quantification of rat volume *in vivo* by magnetic resonance imaging. *Magn. Reson. Med.* **30**, 355–360 (1993).
- J. Caesar, S. Shaldon, L. Chiandussi, L. Guevara, and S. Sherlock: The use of indocyanine green in the measurement of hepatic blood flow and as a test of hepatic function. *Clin. Sci.* **21**, 43–57 (1961).
- D. Z. D'Argenio and A. Schumitzky: "ADAPT User's Guide." Biomedical Simulations Resource, University of Southern California, Los Angeles, CA, 1992.
- E. A. Gehan and S. L. George: Estimation of human body surface area from height and weight. *Cancer Chemother. Rep. Part 1* **54**, 225–235 (1970).
- J. M. Coppelletta and S. B. Wolbach: Body length and organ weights of infants and children. *Am. J. Pathol.* **9**, 55 (1933).
- K. Kayser: "Height and Weight in Human Beings: Autopsy Report." R. Oldenbourg, Munich, Germany, 1987.
- K. Urata, S. Kawasaki, H. Matsunami, Y. Hashikura, T. Ikegami, S. Ishizone, Y. Momose, A. Komiya, and M. Makuchi: Calculation of child and adult liver volume for liver transplantation. *Hepatology* **21**, 1317–1321 (1995).
- D. L. Glaubiger, D. D. von Hoff, and J. S. Holcenberg: The relative tolerance of children and adults to anticancer drugs. *Front. Radiat. Ther. Oncol.* **16**, 42–49 (1982).
- M. J. Gardner and W. J. Jusko: Effect of age and sex on theophylline clearance in young subjects. *Pediatr. Pharmacol.* **2**, 157–169 (1982).
- M. V. Relling, W. R. Crom, J. A. Pieper, G. C. Cupit, G. K. Rivera, and W. E. Evans: Hepatic drug clearance in children with leukemia: changes in clearance of model substrates during remission-induction therapy. *Clin. Pharmacol. Ther.* **41**, 651–660 (1987).
- B. D. Wiegand, S. G. Ketterer, and E. Rapaport: The use of indocyanine green for the evaluation of hepatic function and blood flow in man. *Am. J. Dig. Dis.* **5**, 427–436 (1960).
- G. Engel, U. Hofmann, H. Heidemann, and M. Eichelbaum: Identification and characterization of cytochrome P450 enzymes involved in the biotransformation of antipyrine in man (abstr.). *Z. Gastroenterol.* **32**, 51 (1994).
- G. Engel, U. Hofmann, H. Heidemann, and M. Eichelbaum: Cytochrome P450 2C subfamily plays an important role in the metabolism of antipyrine (abstr.). *Proceedings of the 14th European Workshop on Drug Metabolism*, Paris, France, July 4–8, 1994, p. 282.

23. S. Kawasaki, Y. Sugiyama, T. Iga, M. Hanano, T. Beppu, M. Sugiura, K. Sanjo, and Y. Idezuki: Hepatic clearances of antipyrine, indocyanine green, and galactose in normal subjects and in patients with chronic liver diseases. *Clin. Pharmacol. Ther.* **44**, 217-224 (1988).
24. H. A. Wynne, L. H. Cope, E. Mutch, M. D. Rawlins, K. W. Woodhouse, and O. F. James: The effect of age upon liver volume and apparent liver blood flow in healthy man. *Hepatology* **9**, 297-301 (1989).
25. S. A. Wrighton, W. R. Brian, M.-A. Sari, M. Iwasaki, F. P. Guengerich, J. L. Raucy, D. T. Molowa, and M. Vandenbranden: Studies on the expression and metabolic capabilities of human liver cytochrome P450IIIA5 (HLp3). *Mol. Pharmacol.* **38**, 207-213 (1990).
26. E. Jacqa-Aigrain and T. Cresteil: Cytochrome P450-dependent metabolism of dextromethorphan: fetal and adult studies. *Dev. Pharmacol. Ther.* **18**, 161-168 (1992).
27. C. Cazeneuve, G. Pons, E. Rey, et al.: Biotransformation of caffeine in human liver microsomes from foetuses, neonates, infants and adults. *Br. J. Clin. Pharmacol.* **37**, 405-412 (1994).
28. K. E. Thummel, D. D. Shen, T. D. Podoll, K. L. Kunze, W. F. Trager, C. E. Bacchi, C. L. Marsh, J. P. McVicar, D. M. Barr, J. D. Perkins, and R. L. Carithers: Use of midazolam as a human cytochrome P450 3A probe. II. Characterization of inter- and intraindividual hepatic CYP3A variability after liver transplantation. *J. Pharmacol. Exp. Ther.* **271**, 557-566 (1994).