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Relationships Between Plasma Theophylline Clearance, Liver Volume and Body Weight in Children and Adults

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Summary. The influence of liver volume and body weight on plasma theophylline clearance was investigated in asthmatic children and adults. A linear relationship ($r = +0.99$) was demonstrated between ideal body weight and liver volume estimated by an ultrasonic scanning technique. Age-related changes in liver volume-to-body weight ratio could account for only 30% of differences in plasma theophylline clearance (l/h/kg) between children and adults. It is summized that increased hepatic mixed function oxidase activity is the major contributor to the higher plasma theophylline clearance in children.

Key words: theophylline clearance, asthma; body weight, liver volume, ultrasound

Theophylline clearance on a body weight basis is greater in children than in adults (Ellis et al. 1976; Loughnan et al. 1976). An increased clearance in children has also been documented for drugs of low hepatic extraction such as phenobarbital (Garrettson and Dayton 1970), antipyrine (Alvares et al. 1975) and ethosuximide (Buchanan et al. 1973).

Patterns of urinary theophylline and metabolites are very similar in children and adults indicating that no particular pathway for theophylline metabolism is selectively enhanced in children (Grygiel and Birkett 1980). While it is known that liver volume-to-body weight ratio is higher in children than in adults (Rane and Wilson 1976), the contribution of such age-related anatomical changes to differences in plasma theophylline clearance between these groups has not been previously examined.

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The influence of liver size on plasma clearance of drugs which are extensively metabolised by this organ was first proposed in the 'functional hepatic parenchymal mass' hypothesis (Branch et al. 1975). In support of this view, a positive correlation between liver volume and antipyrine clearance in phenobarbital-induced volunteers was subsequently reported from the same laboratory (Roberts et al. 1976).

Using a noninvasive ultrasound scanning technique to quantitate liver volume in vivo, the relationship of plasma clearance of theophylline to liver volume and body weight is reported.

Materials and Methods

Protocol

Patients from the pediatric (3 males and 2 females, age range 3.5 to 12 years), and adult (3 males and 2 females, age range 19 to 48 years) populations, admitted to the hospital with acute exacerbation of asthma, were maintained at steady-state in the desired therapeutic range with intravenous infusions of theophylline ethylenediamine as clinically required. Steady-state plasma theophylline concentration during a constant infusion was assumed when two plasma samples collected 6 h apart did not differ by more than 10%. In the pediatric group, the first blood sample was drawn 12 h after the start of the infusion while 24 h elapsed prior to the first sample collection in adults.

Patients were excluded from the study if they were outside 10% of their ideal body weight in order to reduce the error of ultrasound liver volume estimation. Congestive cardiac failure, liver disease, cigarette smoking and ingestion of drugs known to affect the hepatic mixed function oxidase enzyme ac-

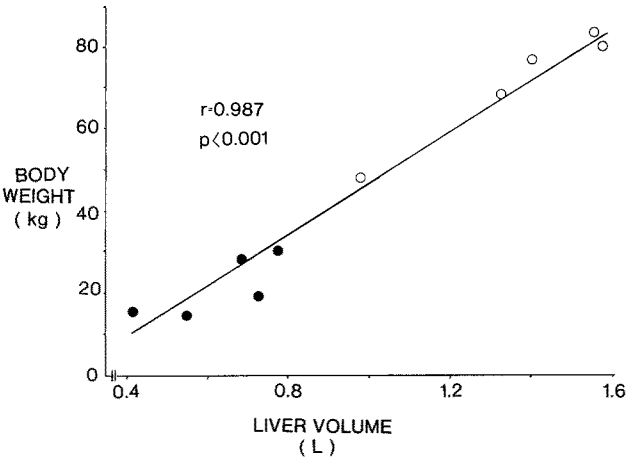

Fig. 1. Correlation between liver volume and body weight in children (closed circles) and adults (open circles)

Table 1. Group characteristics of asthmatic patients

Group	Age (y)	Body weight [kg]	Liver volume [l]	LV/BW ratio[a]
Children	6.3 ± 1.2	21.8 ± 3.2	0.631 ± 0.066	0.030 ± 0.003
Adults	29.0 ± 6.3	70.4 ± 6.2	1.366 ± 0.108	0.0195 ± 0.0030
p	< 0.01	< 0.001	< 0.001	< 0.001

[a] Ratio of liver volume to body weight in units of l/kg. Results are expressed as mean ± SEM

Table 2. Plasma theophylline clearance in asthmatic patients

Group	CL* [l/h]	CL_{BW} [l/h/kg]	CL_{LV} [l/h/l]
Children	2.0 ± 0.3	0.0935 ± 0.0104	3.274 ± 0.523
Adults	2.2 ± 0.3	0.0317 ± 0.0050	1.628 ± 0.238
p	N.S.	< 0.001	< 0.001

CL* is plasma theopylline clearance expressed in units of l/h; CL_{BW} is plasma theophylline clearance adjusted for body weight; Cl_{LV} is plasma theophylline clearance adjusted for liver volume. Results are expressed as mean ± SEM

tivity were other criteria for exclusion. Ultrasound scanning was performed during the period of hospitalisation only when the majority of asthmatic symptoms had subsided.

Data Analysis

Using a specific high performance liquid chromatographic method for quantitating theophylline in plasma described previously (Foenander et al. 1980), the steady-state plasma theophylline concentration was used to determine plasma theophylline clearance by

$$Cl^* = \frac{D}{(C_{ss})}$$

where Cl* is plasma theophylline clearance (l/h), D is the infusion rate of theophylline (mg/h), and C_{ss} is the steady-state plasma theophylline concentration (mg/l). Cl_{BW} is plasma theophylline clearance adjusted for body weight (l/h/kg) and Cl_{LV} is plasma theophylline clearance adjusted for liver volume (l/h/l).

Ultrasound Technique

Using an Octoson ultrasonic scanner (Ausonics Pty. Ltd., Australia), transverse scans were performed with the patient lying prone on the waterbath membrane. Serial sections at 1 cm intervals were carried out from the inferior hepatic margin to above the diaphragm. Scanning time was of the order of five seconds and during this period respiration was arrested in mid-inspiration to maximise the clarity of the superior hepatic margin (Rassmusen 1972). Individual sections were recorded on graded photographic negatives and the area occupied by the liver in each section was calculated by planimetry. Liver volume was given by the sum of all liver areas multipled by the sectional interval (1 cm).

The volume as calculated on a cadaveric liver in vitro was within 2% of actual liver volume on serial estimations and the photographic negatives obtained in these studies were used to graduate the planimeter. Repeated estimations on normal volunteers indicated a variation in liver volume of less than 6%.

Estimations of liver volume on Grey Scale ultrasound have been reported using contact scanner (Rasmussen 1972) but the accuracy of the technique relies heavily on the operator's skill in producing correct sections. With the Octoson waterbath scanner, transducer movement is computer controlled and independent of operator technique. Additionally, scanning times for the Octoson method are shorter than for contact scanning so that even these asthmatic patients had no difficulty arresting respiration for 5 s or less.

Results

The mean data for children and adults is shown in Table 1. The groups were significantly different in age ($p < 0.01$), body weight ($p < 0.001$), and liver volume ($p < 0.001$). A significant difference in the ratio

of liver volume to body weight was found between the groups ($p < 0.01$). As shown in Table 2, there was no difference between the groups in plasma theophylline clearance expressed in units of l/h. However, when adjusted for body weight or for liver volume, plasma theophylline clearance was significantly higher in children than in adults. A strong positive correlation was shwon between liver volume and body weight ($r = +0.987$, $p < 0.001$, Fig. 1).

Plasma theophylline clearance (l/h) did not correlate with age ($r = 0.05$), liver volume ($r = 0.18$) or body weight ($r = 0.24$). A negative correlation found between liver volume and plasma theophylline clearance adjusted for body weight ($r = -0.89$, $p < 0.001$) merely reflects the strong relationship shown to exist between liver volume and body weight.

Discussion

Liver volume estimated by ultrasonic scanning showed a strong linear correlation to body weight ($r = +0.99$, $p < 0.001$). Roberts et al. (1976) reported a similar relationship between liver volume and body weight in uninduced adults who were within 12% of ideal body weight ($r = +0.81$, $p < 0.01$). From the very close relationship between these parameters, it is clear that there is very little variation in liver volume independent of body weight in subjects close to ideal body weight. Children as a group had a 50% higher liver volume on a body weight basis than adults but this accounted for only a small part of the difference in theophylline clearance. Clearance adjusted for body weight (Cl_{BW}) was 300% higher in children than in adults and was still 200% higher when liver volume was taken into account. Thus, the oxidative enzyme activity per unit mass of liver must be two-fold higher in children than in adults.

In this study with uninduced patients ranging in age from 3.5 to 48 years, no relationship was found between liver volume and plasma theophylline clearance (l/h). Similarly, Rylance et al. (1980) were unable to establish a relationship between liver volume and antipyrine clearance in nine uninduced children ($r = +0.173$). In uninduced adult volunteers, the relationship between liver volume and antipyrine clearance reported by Roberts et al. (1976) was of marginal statistical significance and then only when a subject with antipyrine clearance value 2 standard deviations above the mean of the remaining group, was excluded from statistical analysis. Interestingly, in the same group of adults when re-examined following enzyme induction with phenobarbital, plasma antipyrine clearance and liver volume were shown to be linearly related in a positive fashion ($r = +0.86$, $p < 0.01$) but no significant change in liver volume was apparent. These findings could well be interpreted to support the concept that variability in enzyme activity per unit mass of liver is reduced by inducing agents. A marginally significant correlation between in vivo antipyrine clearance ($r = +0.37$, $p < 0.1$) was reported in 20 patients with normal hepatic histology by Pirttiaho (1979). When divided into induced and uninduced groups, the induced group showed a 1.3-fold greater liver weight: body weight ratio but antipyrine clearance was 2.7-fold greater than in the uninduced group. It is clear that variability in oxidative enzyme activity is the major cause of interindividual differences in rates of drug metabolism in vivo and that liver volume is a poor predictor of metabolic drug clearance.

At the time when the 'functional hepatic parenchymal mass' hypothesis was proposed (Branch et al. 1975), there was little evidence for interindividual variability in human hepatic enzyme activity. However, it is now well established from both in vitro and in vivo studies that considerable variation in hepatic enzyme activity exists between individuals (Kapitulnik et al. 1977; Birkett and Conney 1980) so that a simple relationship between liver size and plasma clearance of drugs of low hepatic extraction is unlikely.

Given the simple relationship between liver volume and ideal body weight and the fact that neither parameter correlates with plasma theophylline clearance, it would be predicted that dosage regimens based on body weight would result in variability of plasma theophylline concentrations attained. As this, unfortunately, is the clinical experience, it is proposed that this variability reflects the range of hepatic mixed function oxidase activity.

While there appears to be a linear relationship between liver volume and ideal body weight, it is clear that no simple relationship exists between plasma clearance of theophylline and liver volume or body weight.

References

Alvares AP, Kapelner S, Sass SS and Kappas A (1975) Drug metabolism in normal children, lead-poisoned children and normal adults. Clin Pharmacol Ther 17: 179–182

Birkett DJ, Conney AH (1980) Patterns of drug metabolism. Clin Exp Pharmacol Physiol 6: 171–172

Branch RA, James JA, Read AE (1975) Major determinants of drug disposition in chronic liver disease: A study wigh indocyanine green and antipyrine. Br J Clin Pharmacol 2: 370–371

Buchanan RA, Kinkel AW, Smith TC (1973) The absorption and excretion of ethosuximide. Int J Clin Pharmacol 7: 213–218

Ellis EF, Koysooko R, Levy G (1976) Pharmacokinetics of theophylline in children with asthma. Pediatrics 58: 542–547

Foenander T, Birkett DJ, Miners JO, Wing LMH (1980) The simultaneous determination of theophylline, theobromine and caffeine in plasma by high performance liquid chromatography. Clin Biochem 13: 132–134

Garrettson LK, Dayton PG (1970) Disappearance of phenobarbital and diphenylhydantoin from serum of children. Clin Pharmacol Ther 11: 674–679

Grygiel JJ, Birkett DJ (1980) Effects of age on patterns of theophylline metabolism. Clin Pharmacol Ther 28: 456–461

Kapitulnik J, Levin W, Poppers PJ, Tomaszewski JE, Jerina DM, Conney AH (1976) Comparison of the hydroxylation of zoxazolamine and benzo(a)pyrene in human placenta: Effects of cigarette smoking. Clin Pharmacol Ther 20: 557–564

Loughnan PM, Sitar DS, Ogilvie RI, Eisen A, Fox Z, Neims AH (1976) Pharmacokinetic analysis of the disposition of intravenous theophylline in young children. J Pediatr 88: 874–879

Pirttiaho H (1979) Liver size in evaluating drug metabolising capacity in man. Int J Clin Pharmacol Biopharm 17: 271–276

Rane A, Wilson JT (1976) Clinical Pharmacokinetics in infants and children. Clin Pharmacokinet 1: 2–24

Rasmussen SN (1972) Liver volume determination by ultrasonic scanning. Br J Radiol 25: 579–585

Roberts CJC, Jackson L, Halliwell M, Branch RA (1976) The relationship between liver volume, antipyrine clearance and indocyanine clearance before and after phenobarbitone administration in man. Br J Clin Pharmacol 3: 907–913

Rylance GW, Cowan MD, Guy E, Moreland TA (1980) Antipyrine metabolism and liver volume in children. in: Turner P (ed) Proceedings of the First World Conference on Clinical Pharmacology and Therapeutics, Abstract No. 0567, Macmillan, London, U.K.

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