IMPAIRMENT OF DRUG METABOLISM IN POLYCYSTIC NON-PARASITIC LIVER DISEASE

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- 1 Drug-metabolizing capacity in cases of polycystic non-parasitic liver disease was investigated using plasma antipyrine clearance as an index.
- 2 The four subjects with maternally inherited polycystic liver metabolized antipyrine at a significantly slower rate than the six other members of the family.
- 3 This reduction in antipyrine metabolism is due to the loss of active liver parenchyma, and is probably also influenced by alterations in the vascular bed due to compression by the enlarged cysts.

Introduction

Polycystic liver is a relatively rare congenital disease in which all or part of the organ is filled with thin-walled, fluid-containing cysts of various sizes. The volume of the cysts increases with age, thus causing liver enlargement (Melnick, 1955), and in many cases the symptoms associated with the disease, distension of the right upper abdomen and pain attacks, are due to compression to the adjacent organs (Comfort, Gray, Dahlin & Whitesell, 1952; Melnick, 1955; Peltokallio, 1970). The subjects are otherwise asymptomatic and their liver function usually remains normal (Melnick, 1955; Peltokallio, 1970). Probably for this reason the diagnosis is often made during operation or at autopsy.

Impaired drug metabolism has frequently been associated with patients with parenchymal liver disease (Schoene, Fleischmann, Remmer & von Olderhausen, 1973; Branch, Herbert & Read, 1973; Sotaniemi, Pelkonen, Mokka, Huttunen & Viljakainen, 1977), and the prescription of drugs for a patient with polycystic liver hence evokes the question whether the drug metabolism is altered in such a disease. The problem was investigated by determining plasma antipyrine clearance rates in a family with non-parasitic polycystic liver.

Figure 1 A family with inherited polycystic liver disease. (□ male; ○ female; ■ male polycystic liver; ● female polycystic liver).

Methods

- Subjects

A family with polycystic liver was investigated. The disease had been inherited from the mother by four of the six children (Figure 1), the diagnosis being based on the case history, Tc⁹⁹ liver scan (Figure 2) and

Figure 2 ⁹⁹Tc liver scan (case 1).

hepatic histology (cases 1, 2, 6) obtained at abdominal surgery. The relevant clinical and biochemical data are given in Table 1. A group of 13 patients of similar age distribution were chosen as controls from our series of 200 consecutive patients with liver biopsy (Sotaniemi, Pelkonen, Ahokas, Pirttiäho & Ahlqvist, 1978). All had normal liver architecture. None of the patients involved had any clinical manifestations of heart failure at the time, and their kidney function was normal, as judged by creatinine clearance. Informed consent was obtained before the antipyrine test was performed.

Protocol

The subjects were investigated at the Clinical Research Unit. Blood samples for liver function tests were drawn after an overnight fast, and an oral antipyrine test (20 mg/kg in 100 ml fruit juice) was performed on each subject similarly after a night's fast. Plasma samples for the determination of antipyrine in the blood were obtained at zero time and 1, 3, 6, 9, 12, 24 and 30 h after administration.

Antipyrine assay

Plasma antipyrine was measured by a gas liquid chromatographic method with phenacetin as an internal standard (Prescott, Adjepon-Yamoah & Roberts, 1973), as used earlier (Sotaniemi, Ahlqvist, Pelkonen, Pirttiäho & Luoma, 1977).

Serum biochemistry

Serum concentration of albumin (Alb) and total bilirubin (tot. bil) and aspartate amino transferase (ASAT) and alkaline phosphatase (A-P) activity in the serum were measured using standard Autoanalyzer techniques (Technicon). The thrombotest was applied using an automatic instrument (Thrombolab 702, Stockholm, Sweden).

Calculations

The plasma antipyrine half-life ($T_{1/2}$) was read from the linear portion of the log concentration/time curve. Plasma clearance (Cl) was obtained by dividing the dose by the area under the plasma concentration/time curve calculated by the trapezoidal rule. The apparent volume of distribution (aVd) was calculated from the relationship: $aVd = \text{plasma clearance} / \text{elimination rate constant (k)}$.

The statistical analysis of the data was performed using the Student's *t*-test.

Figure 3 Plasma antipyrine level in a family with polycystic liver disease (mean $\pm$ s.d.). ● polycystic disease; ○ other members of the family.

Results

Antipyrine metabolism was impaired in the four subjects with polycystic liver (Table 1), the plasma half-life was prolonged, the clearance rate decreased, and the volume of distribution of the drug did not diverge from that obtained for the other members of the family and the controls.

Antipyrine absorption was not delayed in the subjects with polycystic liver (Figure 3), for mean plasma antipyrine 1 h after administration did not diverge from the values in the other family members, but the differences in the blood levels of the drug at 6 h and onwards reflect the diverging rate of drug hydroxylation in the groups.

The liver test values of the patients with polycystic liver varied within the normal range, except that case 1 had low serum albumin and high alkaline phosphatase levels (Table 1). There was no correlation between any liver function test and the antipyrine kinetics.

Discussion

Antipyrine is widely used to reflect the hepatic drug-metabolizing capacity in man, since it is completely absorbed when given orally, is only bound to plasma or tissue proteins to a minor extent, is extensively metabolized by the liver enzymes (Brodie & Axelrod, 1950) and is relatively safe (Sotaniemi, Kontturi & Larmi, 1973). The rate of antipyrine elimination from

Table 1 Clinical and biochemical data and results of antipyrine studies in a family with polycystic liver disease and controls

Subject	Age/Sex (years)	Body weight (kg)	Polycystic liver	Liver function tests			ALB	Thrombotest		Antipyrine	
				Tot Bil (μmol/l)	ASAT (U/L)	A-P (U/L)	(g/l)	%	T ₁ (h)	Cl (ml/min)	aVd (l/kg)
1	63/M	62.0	Yes (a,b ⁺)	6	37	531	34	70	14.0	23.2	0.45
2	58/F	69.0	Yes (a,b)	10	34	194	42	100	10.9	22.6	0.31
3	55/M	86.0	No	10	40	129	46	100	11.6	34.0	0.40
4	52/F	57.0	No	7	21	214	41	100	7.4	36.6	0.41
5	48/M	64.0	No	6	27	196	43	100	8.5	44.9	0.51
6	46/F	54.0	Yes (a,b)	9	25	171	41	100	10.6	25.6	0.43
7	44/F	51.0	No	8	18	152	42	100	9.2	29.6	0.46
8	42/M	79.0	Yes (a)	9	26	189	44	100	13.4	29.8	0.44
9	40/F	51.0	No	7	18	139	43	100	4.7	52.1	0.41
10	37/F	49.5	No	10	22	102	43	100	6.8	41.8	0.50
Subjects with polycystic liver (cases 1, 2, 6, 8)											
mean											
s.d.											
Other members of the family (cases 3, 4, 5, 7, 9, 10)											
mean											
s.d.											
Controls, 13											
mean											
s.d.											

+ = Diagnosis of the polycystic liver: a = ⁹⁹Tc-liver scan, b = liver biopsy during abdominal surgery.
 ++ = P-values for the difference between the means (subjects with polycystic liver compared with other members of the family and controls P < 0.01).

the plasma hence accurately reflects the hydroxylation capacity of the liver. The reduced antipyrine clearance shown here in subjects with polycystic liver is thus suggestive of impaired drug metabolizing capacity.

Hepatic drug clearance after oral administration is determined mainly by the liver blood flow, the uptake of the drug by the liver and activity of the drug-metabolizing enzyme system (Wilkinson & Schenker, 1976). Antipyrine extraction by the liver is low, and hence its plasma clearance, assuming a normal structure, is largely independent of the hepatic blood flow (Wilkinson & Shand, 1975). Drug metabolism in a diseased liver is related to the amount and activity of the healthy parenchyma (Sotaniemi, Ahlqvist *et al.*, 1977; Sotaniemi, Pelkonen *et al.*, 1977; Shand, Branch, Wood & Villeneuve, 1978) and is influenced by intrahepatic and extrahepatic shunts (Groszmann, Kraveta & Parysow, 1977). In a polycystic liver the parenchyma is reduced by the volume of the cysts, and the impaired antipyrine metabolism noted here probably reflects this loss of active liver mass. On the other hand, the liver has relatively great reserve capacity, 15–20% of its volume being sufficient to maintain its normal functions, including antipyrine metabolism (Peltokallio, 1970; Sotaniemi, Pelkonen *et al.*, 1977). Our subjects with polycystic liver

showed slow antipyrine metabolism in spite of the fact that only one of them had any abnormal liver tests. This indicates that drug metabolism and liver test deviation do not run parallel in the case of polycystic liver disease. The enlarged cysts may compress the hepatic vascular bed, increase the portal venous pressure (Campbell, Bick, Paulsen, Lober, Watson & Varco, 1958), and lead to the formation of arterio-venous shunts as a consequence of which the availability of antipyrine to the liver near the cysts or between them might be delayed, and this would contribute to the impaired drug metabolism.

Although antipyrine clearance need not necessarily reflect the elimination rate of other compounds as noted in the review by Kalow & Inaba (1976), there is evidence to suggest that an antipyrine test might be predictive of the disappearance rate of compounds such as galactose, lignocaine, paracetamol, bromsulphalein and propranolol (Andreasen, Ranek, Statland & Tygstrup, 1974; Branch & Shand, 1976; Sotaniemi, Anttila, Pelkonen, Järvensivu, Sundquist, 1978). The impaired drug metabolism demonstrated here in the four members of a family with polycystic liver disease as compared with healthy members of the same family and the controls demonstrates the need for care, at least, when prescribing drugs for subjects with polycystic liver.

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