IMPAIRMENT OF HEPATIC DRUG METABOLISM IN ALCOHOLICS

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- 1 The effects of chronic ethanol intake on the elimination kinetics of antipyrine were determined in nineteen male alcoholic subjects with comparison made to fourteen male volunteers.
- 2 Half-lives were longer and clearance values less in the alcoholic group.
- 3 Significant rank correlations were found between half-life and clearance when compared with various biochemical parameters of liver function measured in the plasma of the alcoholics.
- 4 These results show that a significant proportion of the alcoholics studied had impaired hepatic drug metabolizing capacity and that the activity of hepatic microsomal enzymes may be related to the extent of ethanol induced liver damage in these subjects.

Introduction

It is well known that severe liver disease causes impairment of hepatic drug metabolizing enzymes (Branch, Herbert & Read, 1973; Andreassen, Ranek, Statland & Tygstrup, 1974). However, there is uncertainty as to the effect of lesser degrees of hepatic impairment on this particular function. The present study was undertaken to determine the effects of chronic ethanol intake on the activity of hepatic drug metabolizing enzymes in a group of alcoholics with no previous history of liver disease.

Antipyrine was chosen as the test drug as its elimination kinetics have been widely used to assess the activity of hepatic microsomal drug metabolizing enzymes in man (Stevenson, 1977). It has properties that seem to make it ideal for this purpose. The drug is completely absorbed in the gastro-intestinal tract and metabolized almost completely in the liver (Brodie & Axelrod, 1950). Since clearance of antipyrine is slow, changes in liver blood flow due to hepatic injury are unlikely to alter the rate of elimination of the drug (Branch, Shand, Wilkinson & Nies, 1974). In addition, saliva can be used as a non-invasive alternative to plasma sampling for the determination of its elimination kinetics (Welch, De Angelis, Wingfield & Farmer, 1975; Vesell, Passananti, Glenwright & Dvorchik, 1975).

Methods

Subjects

Nineteen male patients, aged 23 to 66 years (mean $\pm$ s.d. 43 ± 11), who were the management of an

Alcohol and Drug Addicts Treatment Unit, were studied. Each one of them had had a drinking problem for more than 8 years. Although an accurate figure for daily alcohol consumption could not be obtained from the subjects, it was estimated that this value ranged from 100–1560 g. Most of the alcohol was taken in the form of beer, fortified wines or spirits. One subject had been taking 200 mg phenytoin per day for epilepsy. The only other medication administered to the subjects was chlormethiazole (Hemineurin), the maximum daily dose of this agent being 3200 mg. Control data was obtained from fourteen healthy male volunteers, aged 21 to 69 years (mean $\pm$ s.d. 31 ± 14), who were not on any medication at the time of the study. These control subjects consumed alcohol occasionally on a social basis.

Protocol

After an overnight fast, antipyrine was administered to each patient in a dose of 10 mg/kg body weight dissolved in water. Saliva specimens were collected prior to and 3, 6, 9, 12, 24 (and in most cases), 36 h after drug administration. Samples were centrifuged to remove foreign particles and stored at -15°C until analysed. Antipyrine in saliva was assayed by a gas-liquid chromatographic method described previously (Harman, Penhall, Priestly, Frewin, Phillips & Clarkson, 1977). A 10 ml blood sample was taken prior to drug administration and alkaline phosphatase, lactate dehydrogenase, aspartate transaminase, bilirubin, albumin and globulin were determined in plasma by standard laboratory procedures.

Calculations

The elimination rate constant (K_{el}) of antipyrine was calculated from the slope of the linear portion of the concentration-time curve. The half-life ($T_{1/2}$) was determined as ($T_{1/2}=0.693/K_{el}$).

The apparent volume of distribution (V_d) was calculated using the notation ($V_d=D/C_0$) (ml/kg), where D was the dose (mg/kg) and C_0 was the apparent initial concentration. Clearance of antipyrine (CR) for each subject was calculated as $CR=V_d \cdot BW \cdot K_{el}$ (ml/min), where BW was the body weight.

The Mann-Whitney U-test for unrelated samples and the Spearman rank correlation test were used for statistical analysis of the data. Multiple regression was performed using the SPSS Program (Subprogram Regression).

Results

Table 1 shows the relevant clinical and biochemical data obtained in the nineteen alcoholic patients. The values for the three parameters used to evaluate kinetics of antipyrine measured in the saliva of the nineteen alcoholic subjects were compared with those obtained from fourteen controls. Half-lives of

antipyrine in the alcoholic subjects ranged from 7.3 to 38.0 h (median=15.2) and were greater than in controls, which ranged from 7.7 to 16.5 h (median=11.5, $P=0.031$). Our control values are comparable with those obtained in control subjects in previous studies (Stevenson, 1977). The values for antipyrine clearance were less in the alcoholic group, range 21.1 to 89.1 ml/min (median 40.2), than in controls, range 39.4 to 97.6 ml/min (median=55.6, $P=0.019$). There was no difference in the apparent volumes of distribution in the two groups ($P=0.067$). Significant rank correlations were found for both antipyrine half-life and clearance when compared with lactate dehydrogenase, aspartate transaminase activities, conjugated bilirubin, albumin and globulin (Table 2). An increase in total bilirubin correlated with an increase in half-life, but not with reduced clearance. Multiple regression was used to relate these biochemical liver function tests in combination as predictors of antipyrine half-life. Aspartate transaminase activity was found to contribute 35%, globulin level 13% and albumin level 6% to the variance explained when antipyrine half-life was significantly predicted ($F=6.10$ with 3, 15 df, $P=0.006$) by the following equation: antipyrine half-life = $56.8 + 18.7$ (log aspartate transaminase activity) -1.0 (albumin level) -0.7 (globulin level). The coefficients were all significant at $P < 0.05$. The other

Table 1 Pharmacokinetic data for antipyrine and the results of hepatic function tests in the nineteen alcoholic subjects

Subject	$T_{1/2}$ (h)	CLR (ml/min)	V_d (ml/kg)	AST (IU/l)	LDH (IU/l)	ALP (IU/l)	Conj Bili (μ mol/l)	Total Bili (μ mol/l)	Alb (g/l)	Glob (g/l)
1	7.3	85.8	675	18	195	136	2	10	49	27
2	7.4	87.5	800	15	188	88	1	16	45	33
3	8.4	77.5	834	9	193	78	1	6	51	20
4	9.1	57.8	755	11	225	43	1	5	58	13
5	10.0	89.1	857	18	231	82	1	7	48	22
6	10.5	44.0	528	43	223	60	2	16	51	31
7	11.9	51.4	793	23	198	102	2	10	34	39
8	14.0	40.4	619	29	197	53	2	28	46	31
9	15.0	30.6	696	67	270	77	1	9	41	36
10	15.2	41.0	768	17	229	99	2	13	36	39
11	16.7	31.2	685	63	257	75	3	20	40	34
12	16.8	37.5	779	50	208	87	2	8	46	34
13	19.1	40.2	923	170	283	137	10	35	42	45
14	21.1	33.1	830	39	217	73	6	27	40	40
15	21.7	27.0	890	39	204	151	3	20	41	37
16	22.1	28.2	730	92	313	100	6	22	40	42
17	26.2	39.0	1107	32	252	76	5	19	44	36
18	29.2	35.3	1102	92	261	106	3	16	40	40
19	38.0	21.1	989	49	253	74	2	9	40	25

Normal range

5-40 140-300 25-95 1-4 6-24 34-44 24-42

$T_{1/2}$ —half-life; CLR—clearance; V_d —apparent volume of distribution; AST—aspartate transaminase; LDH—lactate dehydrogenase; ALP—alkaline phosphatase; Bili—bilirubin; Alb—plasma albumin; Glob—plasma globulins.

tests contributed little to the variance explained and their regression coefficients were not statistically significant. These variables were therefore excluded from the regression analysis.

Discussion

Chronic ethanol intake in man has been shown to result in increased hepatic enzyme activity (Rubin & Lieber, 1968), resulting in accelerated elimination of such drugs as ethanol, meprobamate, pentobarbital (Misra, Lefevre, Ishii, Rubin & Lieber, 1971), and antipyrine (Vesell, Page & Passananti, 1971). However, prolonged ethanol consumption can eventually result in liver damage, resulting in decreased hepatic enzyme activity (Feinman & Lieber, 1974; Andreasen, *et al.*, 1974). Sotaniemi, Ahlqvist, Pelkonen, Prittiaho & Luoma (1977) found that the ability of the liver to metabolize drugs in alcoholics was related to ethanol-induced changes in the liver. The rate of drug metabolism decreased as the amount of hepatic injury increased. These findings substantiated those of Schoene, Fleischmann, Remmer & von Oldershausen (1972), who found that needle biopsy samples from mild and moderate hepatitis patients of various aetiologies, some of whom were alcoholics, had normal values of cytochrome P450 content, NADPH-cytochrome P450 reductase, aminopyrine-N-demethylase and p-nitroanisole-O-demethylase activities, but that these were decreased in severe hepatitis and cirrhosis.

Nine of the nineteen alcoholics in this study had antipyrine half-lives above the normal range of the controls. This suggests an impaired capacity of the liver to metabolize antipyrine in these individuals. The rise in antipyrine half-life was found to correlate with elevation of lactate dehydrogenase, aspartate transaminase, conjugated bilirubin, total bilirubin, and globulin, and inversely correlate with albumin (Table 2). Thus it appears that, as liver damage progresses, the activity of the hepatic microsomal enzymes decreases concomitantly. These findings are

consistent with those of Sotaniemi *et al.* (1977) and were confirmed to some extent by the multiple regression analysis, which showed that aspartate transaminase activity, albumin and globulin levels could be used to predict antipyrine half-life in these subjects.

In our study, it was not possible to determine the severity of liver damage by needle biopsy sampling. However, the results of the biochemical tests of liver function in these alcoholics indicate an apparently mild degree of hepatic impairment in some. The values of aspartate transaminase and alkaline phosphatase activities were, in approximately 50% of cases, either outside or at the upper end of the 95% confidence limits of the normal range. These values are considerably less than those found in a group of subjects with severe alcoholic cirrhosis in which antipyrine metabolism was markedly impaired (Harman *et al.*, 1977). One explanation for the present findings is that our alcoholic subjects are suffering from more severe hepatic impairment than the biochemical tests suggest. However, these results contrast with those of Mezey (1976), who found evidence of enzyme induction in alcoholics, and Kater, Roggin, Tobin, Zieve & Iber (1969), who demonstrated that alcoholic patients had an increased rate of metabolism of drugs.

One aspect of this study which proved difficult to control was the nutritional status of the alcoholics. Diet has now been shown to influence drug metabolism (Kappas, Anderson, Correy & Alvares, 1976) and must be considered in analysing the results obtained. It is, however, worth noting that all the alcoholic subjects had serum albumin levels which were either within the standard range or above it, the highest value for this parameter being recorded in those subjects with relatively normal hepatic biochemistry. The mechanism for this increase in albumin levels is unclear and needs further evaluation. It is also worth noting that the subjects studied in this series were being treated for alcoholism, not liver disease, and hence it is tempting to speculate that there may be a significant proportion of alcoholics in the community with severely impaired hepatic drug

Table 2 Spearman rank correlations between antipyrine half-life and clearance and various biochemical parameters in the nineteen alcoholic subjects.

	AST	LDH	ALP	Conj Bili	Total Bili	Alb	Glob
Half-life	0.70	0.63	0.09*	0.67	0.57	-0.59	0.57
Clearance	-0.72	-0.54	-0.01*	-0.80	-0.39*	0.58	-0.48**

* $P > 0.05$; ** $0.05 > P > 0.02$

AST—aspartate transaminase; LDH—lactate dehydrogenase; ALP—alkaline phosphatase; Bili—bilirubin; Alb—plasma albumin; Glob—plasma globulins.

metabolizing capacity and undiagnosed liver disease. Measurement of the elimination kinetics of antipyrine in saliva may therefore provide a useful means of determining incipient liver disease in alcoholic subjects.

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(Received November 14, 1977)