

Impaired oxidation of debrisoquine in patients with perhexiline liver injury

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SUMMARY Perhexiline maleate is an antianginal agent which depends on hepatic oxidation for its elimination. Its use may be complicated by the development of peripheral neuropathy and liver damage. The majority of patients with perhexiline neuropathy have an impaired ability to effect metabolic drug oxidation which is genetically determined. Information has not been available on drug oxidation capacity in patients with perhexiline liver injury. Drug oxidation was measured using an oxidation phenotyping procedure in four patients with perhexiline liver injury and in 70 patients with chronic liver disease serving as a control group. All four patients with perhexiline liver damage showed a substantial metabolic defect; three of the four patients (75%) showed a genetically determined impairment of oxidation capacity. The incidence of severely impaired oxidation capacity in the perhexiline group was significantly greater than in the patients with chronic liver disease (6/70; 8.6%) and in the healthy population (9%) ($F=0.0048$). A clear association exists between perhexiline liver injury and diminished drug metabolic activity, suggesting that the propensity to develop perhexiline liver injury is, at least in part, genetically determined.

Perhexiline maleate (Pexid) has been used for the treatment of angina pectoris since 1974. Although clinical trials have shown its undoubted efficacy,¹⁻³ its use is associated with serious side effects such as weight loss,^{4,5} hypoglycaemia,⁶ proximal myopathy,⁷ peripheral neuropathy^{8,9} and hepatic damage.¹⁰⁻¹² The neuropathy and the hepatic damage may not reverse when the drug is withdrawn and deaths have been recorded.¹¹⁻¹⁸

Severe adverse reactions follow the use of perhexiline in only a percentage of patients and are perhaps associated with impaired metabolism of the drug. Perhexiline is a lipophilic drug and its elimination depends on hepatic oxidation to the more polar monohydroxylated and dihydroxylated metabolites.¹⁹ Several drug oxidations in man are under single gene control and exhibit genetic polymorphism.^{20,21} Oxidation is regulated by two alleles, D^H-rapid and extensive oxidation and D^L-slow impaired oxidation.²¹ Individuals homozygous for the D^L allele have an impaired ability to oxidise many drugs. Studies indicate that 9% of the British

white population have a genetically determined inability to effect metabolic drug oxidation.²¹ For technical reasons drug oxidising ability cannot be measured using perhexiline but is readily determined using debrisoquine.^{21,22} It has been shown recently that the majority of patients who develop perhexiline neuropathy show impaired drug oxidising ability suggesting that the susceptibility to perhexiline neuropathy is largely genetically determined.²³ No study of a similar nature has been undertaken in patients with perhexiline related liver injury.

This paper reports the results of oxidation phenotyping in four patients with perhexiline liver injury. Liver damage itself may be associated with impaired oxidation capacity²⁴ thus 70 patients with chronic liver disease were studied as a control group. Patients with alcohol related liver injury were excluded from the control group because an individual's susceptibility to develop alcohol related liver injury is probably at least in part genetically determined. Although ethanol is metabolised mainly by the alcohol dehydrogenase pathway there is evidence to suggest that at high ethanol concentrations the P 450 system contributes.²⁵ It is conceivable that a genetic impairment of oxidation

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capacity might predispose to alcohol related liver injury.

Case histories

TB, a man aged 54 years, was admitted in March 1980 with a six week history of episodes of giddiness and loss of consciousness. He had recently lost weight. His angina had been treated since early 1977 with perhexiline, 300 mg daily. He had never abused alcohol and his weekly intake averaged less than 20 g. He had taken anticoagulants for several years.

On examination there were signs of mitral stenosis and incompetence, of an old left hemiplegia, and of a sensory peripheral neuropathy. The liver was enlarged 5 cm below the right costal margin.

Investigations on admission showed: serum bilirubin $17\ \mu\text{mol/l}$; $1\ \text{mg}/100\ \text{ml}$ (reference range $5\text{--}17\ \mu\text{mol/l}$; $0\cdot3\text{--}1\ \text{mg}/100\ \text{ml}$), serum aspartate transaminase (AST) $127\ \text{U/l}$ ($5\text{--}40$), serum alkaline phosphatase (ALP) $196\ \text{U/l}$; $28\ \text{KAu}/100\ \text{ml}$ ($30\text{--}110\ \text{U/l}$; $3\text{--}13\ \text{KAu}/100\ \text{ml}$), plasma albumin $31\ \text{g/l}$; $3\cdot1\ \text{g}/100\ \text{ml}$ ($35\text{--}50\ \text{g/l}$; $3\cdot5\text{--}5\cdot0\ \text{g}/100\ \text{ml}$), prothrombin time (PT) (off warfarin), 15s (control 13s), serum HBsAg, smooth muscle (SMA), mitochondrial (AMA) and nuclear (ANF) antibodies negative, serum creatinine $107\ \mu\text{mol/l}$; $1\cdot3\ \text{mg}/100\ \text{ml}$ ($60\text{--}120\ \mu\text{mol/l}$; $0\cdot7\text{--}1\cdot4\ \text{mg}/100\ \text{ml}$). Liver biopsy showed a micronodular cirrhosis with extensive liver cell necrosis, inflammation, and Mallory's hyaline.

Perhexiline was stopped in April 1980, but the patient died in March 1981 following a massive gastrointestinal haemorrhage from oesophageal varices.

DW, a woman aged 72 years, was admitted in April 1981, with a six month history of anorexia, weight loss, proximal muscle weakness and numbness and tingling in her feet. Her angina had been treated for seven months before admission with perhexiline, 200 mg daily. She had never abused alcohol and her weekly intake averaged less than 5 g.

On examination there was severe proximal muscle weakness and a sensory peripheral neuropathy. Her liver was not enlarged.

Investigations on admission showed: bilirubin $10\ \mu\text{mol/l}$ ($0\cdot6\ \text{mg}/100\ \text{ml}$), AST $288\ \text{U/l}$, ALP $76\ \text{U/l}$ ($11\ \text{KAu}/100\ \text{ml}$), albumin $34\ \text{g/l}$ ($3\cdot4\ \text{g}/100\ \text{ml}$), PT 14s, HBsAg, SMA, AMA, ANF negative, creatinine $92\ \mu\text{mol/l}$ ($1\cdot0\ \text{mg}/100\ \text{ml}$). Liver biopsy showed a moderately severe hepatitis with a mild degree of fatty infiltration and scanty Mallory's hyaline in the periportal areas.

Perhexiline was withdrawn; her clinical condition

improved and five months later her liver function tests were normal apart from an AST value of $54\ \text{U/l}$.

SP, a woman aged 53 years, was admitted in September 1981, with a three month history of anorexia and abdominal distension. Her angina had been treated with perhexiline, 300 mg daily for the previous three years. Acebutolol 200 mg daily controlled her essential hypertension. She had always been teetotal.

On examination her liver was enlarged 7 cm below the right costal margin and the spleen tip could be felt.

Investigations on admission showed: bilirubin $17\ \mu\text{mol/l}$ ($1\ \text{mg}/100\ \text{ml}$), AST $490\ \text{U/l}$, ALP $112\ \text{U/l}$ ($16\ \text{KAu}/100\ \text{ml}$), albumin $36\ \text{g/l}$ ($3\cdot6\ \text{g}/100\ \text{ml}$), PT 17s, HBsAg, SMA, AMA, ANF negative, creatinine $72\ \mu\text{mol/l}$ ($0\cdot8\ \text{mg}/100\ \text{ml}$). Liver biopsy showed a micronodular cirrhosis with necrosis, inflammation and numerous Mallory bodies (Fig. 1).

Perhexiline was withdrawn; six months later the patient was clinically improved, the liver function tests showed only minimal abnormalities but the hepatosplenomegaly was unchanged.

AG, a woman aged 69 years, was admitted in January 1982 with a three month history of anorexia, weight loss and abdominal distension. Her angina had been treated for three years with perhexiline, 300 mg daily. She had never abused alcohol and drank minimal quantities at Christmas time only.

On examination she was mildly jaundiced and the liver was enlarged 10 cm below the right costal margin. There was moderate ascites and a mild sensory peripheral neuropathy.

Investigations on admission showed: bilirubin $21\ \mu\text{mol/l}$ ($1\cdot2\ \text{mg}/100\ \text{ml}$), AST $213\ \text{U/l}$, ALP $256\ \text{U/l}$ ($36\ \text{KAu}/100\ \text{ml}$), albumin $29\ \text{g/l}$ ($2\cdot9\ \text{g}/100\ \text{ml}$), PT 19s, HBsAg, SMA, AMA, ANF negative, creatinine $64\ \mu\text{mol/l}$ ($0\cdot7\ \text{mg}/100\ \text{ml}$). Liver biopsy showed a micronodular cirrhosis with massive accumulation of Mallory bodies and associated neutrophils, but only very mild fatty change (Fig. 2).

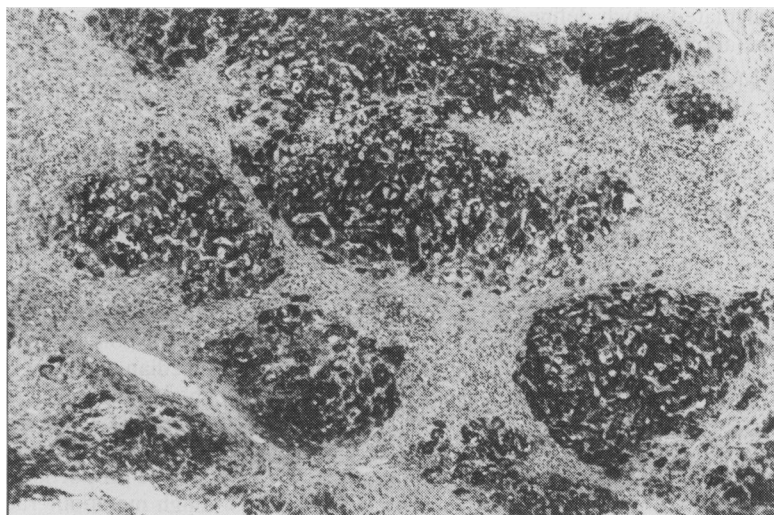
Perhexiline was withdrawn but the patient developed increasing hepatocellular failure and died one month after admission.

Methods

PATIENTS

The study group comprised the four patients with perhexiline liver damage. The control group comprised 70 inpatients/outpatients with biopsy proven chronic liver disease. Patients were excluded from the control group if they had alcohol related

Fig. 1 Liver biopsy from a 53 year old woman who had taken perhexiline, 300 mg daily for three years. Darker nodules containing numerous inflammatory cells are seen in paler connective tissue. Periodic acid - Schiff $\times 75$ (original magnification)



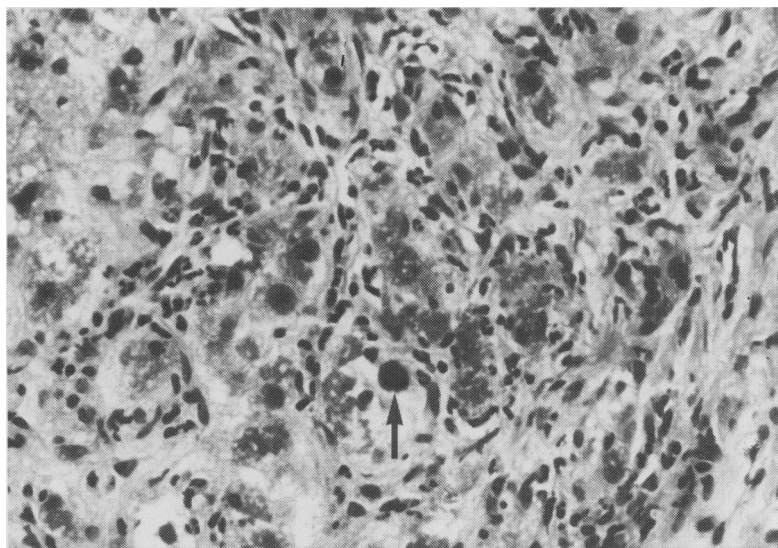
liver disease, were HBsAg positive, had experienced recent severe gastrointestinal haemorrhage or showed evidence of hepatic encephalopathy or renal failure. Patients with ascites were not studied until their fluid retention had been successfully treated.

In both study and control patients a careful note was made of smoking and drinking habits and of concomitant medication. Prothrombin time, routine liver function tests and plasma creatinine values were measured in all patients using standard

laboratory techniques.

All patients were phenotyped for oxidation status using debrisoquine. After an overnight fast a single 10 mg oral dose of debrisoquine (Declinax 10, Roche) was taken. The urine passed in the subsequent eight hours was collected in bulk, the volume measured and a 20 ml sample stored at -20°C until analysis. Each sample was analysed for its content of parent drug and its major metabolite, 4-hydroxydebrisoquine using electron capture gas chromatography. For each patient a metabolic ratio was

Fig. 2 Liver biopsy from a 69 year old woman who had taken perhexiline, 300 mg daily for three years. Swollen hepatocytes contain abundant Mallory bodies (arrowed); there are numerous segmented leucocytes. Haematoxylin and eosin $\times 450$ (original magnification)



calculated which defined that individual's ability to metabolise the drug:

Debrisoquine metabolic ratio

$$= \frac{\% \text{ excreted as unchanged debrisoquine}}{\% \text{ excreted as 4-hydroxy-debrisoquine}}$$
 in the 0–8 hour urine.

Values less than 1 represent extensive oxidation capacity (EM phenotype), while values greater than 12.6 indicate grossly impaired ability as found in individuals homozygous for the D^L allele (PM phenotype).²² Intermediate ratios indicate varying degrees of impairment.

In all subjects studied routine biochemical tests and oxidation phenotyping were performed in the same 24 hour period.

Correlations between variables were performed by linear least squares regression analysis.

Results

The perhexiline study group comprised three women and one man, mean age 62 years. One female patient smoked, none abused alcohol and most took other medication. The length of treatment and the total dose of perhexiline consumed, the clinical and histological features of toxicity and outcome after drug withdrawal varied (Table 1). In three patients (TB, DW, and SP) debrisoquine phenotyping was undertaken at least eight weeks after perhexiline was withdrawn at which time liver function was improving. In the remaining patient (AG) phenotyping was undertaken one week after drug withdrawal when liver function was deteriorating. All four patients showed metabolic ratios

>1; three patients (75%) were phenotypically PM with ratios >12.6 (Table 2).

The control group comprised 54 women and 16 men (3F:1M), mean age 49.6 years. Their liver disease varied in aetiology and severity. Thirteen patients had cryptogenic cirrhosis, 27 primary biliary cirrhosis, 24 chronic active hepatitis and six miscellaneous liver diseases; none was severely decompensated. Very few patients smoked and none abused alcohol (Table 3). The majority took prescribed medication including prednisolone (17 patients) and d-penicillamine (10 patients). The metabolic ratios in the control group ranged from 0.1 to 45.1 with a median value of 1.2. Thirty two patients (45.7%) had a ratio of <1, while six (8.6%) had ratios >12.6. The remaining 32 patients (45.7%) showed intermediate values (Table 3).

The proportion of patients in the study group with high metabolic ratios (3/4) was significantly greater than in the control group (6/70) (Fischer's exact probability $F=0.0048$). Urinary recoveries of debrisoquine and its metabolite were comparable in the perhexiline study group and in controls.

In the control group no correlation existed between the metabolic ratio and the age or sex of the patient or with any particular pattern of cigarette or drug ingestion. Equally no significant relationship existed between the metabolic ratio and values for serum bilirubin ($r=-0.014$; $p>0.1$), serum AST ($r=-0.014$; $p>0.1$), serum ALP ($r=-0.086$; $p>0.1$), plasma albumin ($r=-0.206$; $0.1>p>0.05$) or PT ($r=0.222$; $0.1>p>0.05$).

Discussion

Although a dose dependent increase in trans-

Table 1 Clinical and treatment details of four patients with perhexiline liver injury

Patient	Age (yr)	Sex	Alcohol	Cigarettes daily	Other drugs	Length of treatment (months)	Total dose (g)	Weight loss (kg)	Neuro-pathy	Liver lesion	Outcome after drug withdrawal
TB	54	M	—	—	Warfarin Spironolactone Salbutamol	39	342	6	+	Micronodular cirrhosis + severe hepatitis	Died 11 months later
DW	72	F	—	—	Nitrates	7	42	12	+	Moderate hepatitis with fat + hyaline	Improved
SP	53	F	—	20	Acebutolol	36	329	2	0	Micronodular cirrhosis + severe hepatitis	Improved
AG	69	F	—	—	Nitrates	36	329	7	+	Micronodular cirrhosis + severe hepatitis	Died one month later

Table 2 Results of debrisoquine phenotyping in relationship to discontinuation of drug treatment and liver function in four patients with perhexiline liver injury

Patient	Weeks between drug withdrawal and phenotyping	Serum bilirubin $\mu\text{mol/l}$ (5-17)*	Serum AST U/l (5-40)	Serum ALP U/l (30-110)	Plasma albumin g/l (35-55)	PT s (control=13)	Serum creatinine $\mu\text{mol/l}$ (60-120)	Debrisoquine metabolic ratio
TB	8	10	67	234	24	18 (on Warfarin)	107	2.6
DW	21	3	54	55	38	14	87	24.9
SP	24	15	60	150	38	15	70	22.7
AG	1	21	252	337	24	21	64	66.6

* Reference range in parenthesis. AST, aspartate transaminase; ALP, alkaline phosphatase; PT, prothrombin time. Bilirubin: $\mu\text{mol/l} \times 0.585 = \text{mg}/100 \text{ ml}$. ALP: $\text{U/l} \times 0.141 = \text{KAU}/100 \text{ ml}$. Albumin: $\text{g/l} \times 0.1 = \text{g}/100 \text{ ml}$. Creatinine: $\mu\text{mol/l} \times 0.0113 = \text{mg}/100 \text{ ml}$.

aminase values was observed in the first clinical trials with perhexiline,^{4, 26} the demonstration of histological liver injury is more recent.^{10, 27, 28} Liver injury ranges from minimal non-specific hepatitis¹¹ to micronodular cirrhosis with superimposed features suggesting acute alcoholic hepatitis.^{10, 12, 13, 15-18, 29, 30} The course of the liver disease is variable; usually transaminase values return to normal within a month of perhexiline withdrawal^{4, 31} although in some patients the liver lesion progresses despite withdrawal of the drug.¹¹ The mortality in patients who develop cirrhosis is high.¹¹⁻¹⁸

The incidence of liver injury during prolonged treatment with perhexiline is unknown. Following 600 mg of perhexiline daily for several months, transaminase values invariably rise;²⁷ at a dosage of 200-300 mg per day, the currently recommended therapeutic range, 25-50% of patients show a transient rise in transaminase values. More sensitive

tests, however, reveal a higher degree of abnormalities with 50-75% of patients showing increased serum bile acid values and increased retention of bromsulphalein (BSP) after three months to two years treatment.^{32, 33} The incidence of histological liver damage is difficult to assess because few patients are biopsied. Poupon *et al*³³ for example, studied 46 patients on maintenance perhexiline and found hepatomegaly in 13% (6/46), raised serum bile acid values in 57% (26/46) abnormal BSP retention in 74% (34/46) but evidence of histological damage in all 11 patients in whom liver biopsy was undertaken. In the series reported to date 18 patients have shown non-specific hepatitis with or without fatty infiltration,^{11, 27, 33-5} two a granulomatous hepatitis,^{35, 36} 17 an acute or subacute hepatitis closely resembling acute alcoholic hepatitis,^{8, 11, 14, 15, 27, 28, 37-41} and 14 a micronodular cirrhosis with superimposed 'alcoholic' hepatitis.^{10-13, 15-18, 29, 30}

Table 3 Details and results in the control group of patients with chronic liver disease

Case no	Age, sex	Type of liver disease*	Cigarettes daily	Alcohol consumption	Serum bilirubin $\mu\text{mol/l}$ + (5-17)	Serum AST U/l (5-40)	Serum ALP U/l (30-110)	Plasma albumin g/l (35-50)	PT s (control =13)	Serum creatinine $\mu\text{mol/l}$ (60-120)	Debrisoquine metabolic ratio
1	52 F	CC	—	—	5	46	50	46	14	72	0.1
2	58 F	PBC	—	—	9	57	232	39	12	63	0.1
3	31 F	CAH	—	—	8	28	82	47	13	110	0.2
4	51 M	PBC	—	—	18	49	146	36	16	75	0.2
5	33 M	CAH	—	—	18	30	90	41	16	71	0.2
6	38 M	Haem	—	—	8	28	82	47	13	110	0.2
7	45 F	CC	—	—	16	14	112	31	18	73	0.3
8	61 F	PBC	—	—	18	69	411	40	13	99	0.3
9	64 F	CAH	—	—	6	32	131	46	13	93	0.4
10	65 F	PBC	—	—	9	35	232	38	13	66	0.4
11	61 M	Halothane	—	—	9	30	63	46	13	95	0.4
12	22 M	Wilson's	—	—	18	28	72	44	13	79	0.5
13	70 M	PBC	—	—	86	163	820	39	12	115	0.5

continued over

Table 3 – continued

Case no	Age, sex	Type of liver disease*	Cigarettes daily	Alcohol consumption	Serum bilirubin $\mu\text{mol/l}$ + (5–17)	Serum AST U/l (5–40)	Serum ALP U/l (30–110)	Plasma albumin g/l (35–50)	PT s (control = 13)	Serum creatinine $\mu\text{mol/l}$ (60–120)	Debriso-quine metabolic ratio
14	53 F	PBC	10	—	10	132	534	40	13	102	0.5
15	43 F	CAH	40	—	17	52	242	40	13	73	0.5
16	68 F	PBC	—	—	53	90	1200	40	13	67	0.6
17	52 F	CAH	—	—	9	92	105	45	13	84	0.6
18	56 F	CAH	—	—	12	42	191	41	14	66	0.7
19	40 F	PBC	20	—	90	285	409	40	13	39	0.7
20	50 F	PBC	—	—	30	45	114	43	13	55	0.7
21	64 F	CAH	—	—	7	20	74	46	14	60	0.7
22	63 F	PBC	—	—	173	189	1105	36	13	121	0.7
23	51 F	PBC	—	—	13	34	325	37	13	55	0.8
24	58 F	PBC	—	—	18	94	1200	40	12	87	0.8
25	64 F	CAH	3	—	9	353	114	42	15	86	0.8
26	16 M	Septal	10	—	31	40	157	43	14	69	0.9
27	61 F	PBC	—	—	13	57	350	37	13	50	0.9
28	66 F	PBC	10	—	9	30	283	41	12	90	0.9
29	33 F	CAH	—	—	6	57	184	21	16	77	0.9
30	37 F	CC	—	—	9	31	76	43	15	65	1.0
31	41 F	CC	—	—	14	55	107	36	15	69	1.0
32	46 F	CAH	—	—	12	19	45	40	15	70	1.0
33	60 F	PBC	—	—	32	142	760	34	17	56	1.1
34	23 F	Wilson's	—	—	16	13	43	46	14	72	1.1
35	57 F	CC	—	—	19	32	96	36	16	107	1.1
36	70 F	CAH	—	—	77	33	44	36	14	125	1.2
37	63 F	PBC	—	—	308	133	518	30	16	86	1.2
38	20 F	Wilson's	—	—	7	29	110	38	15	65	1.2
39	34 M	CAH	—	—	42	215	192	32	17	79	1.3
40	31 M	CAH	—	—	14	36	100	43	17	93	1.3
41	67 F	CC	—	—	42	28	169	43	14	86	1.4
42	49 M	CAH	—	—	17	128	100	46	15	77	1.6
43	57 F	CAH	—	—	11	228	72	40	14	79	1.7
44	41 M	CAH	—	—	25	35	246	28	17	80	2.0
45	63 F	PBC	—	—	11	64	459	41	12	62	2.1
46	43 F	CC	—	—	9	55	216	35	14	63	2.1
47	49 F	PBC	—	—	48	159	592	34	14	72	2.3
48	63 F	CAH	—	—	13	539	272	31	11	57	2.6
49	61 F	CC	—	—	5	119	118	42	13	72	2.7
50	57 F	PBC	—	—	25	55	275	34	15	100	2.7
51	65 F	PBC	—	—	86	103	935	26	16	71	2.8
52	49 F	CAH	—	—	8	22	325	38	14	105	3.1
53	61 F	PBC	—	—	309	192	1765	34	13	84	3.1
54	39 F	PBC	—	—	58	144	1020	36	13	63	3.2
55	65 F	CAH	10	—	49	269	269	25	21	97	3.2
56	51 F	PBC	—	—	5	32	313	39	12	83	3.7
57	56 F	CAH	—	—	9	24	55	45	13	88	4.6
58	60 F	PBC	—	—	13	89	446	42	12	72	5.1
59	34 F	PBC	—	—	74	93	326	33	15	64	5.3
60	45 M	CC	—	—	9	89	88	24	21	82	6.2
61	31 F	CC	—	—	37	126	256	23	21	57	6.8
62	27 F	CAH	—	—	68	196	267	20	22	109	7.8
63	44 F	CC	—	—	51	68	241	27	18	61	8.4
64	28 F	CAH	—	—	26	48	103	36	18	65	8.8
65	63 M	PBC	—	—	36	118	612	31	15	101	13.7
66	54 M	CC	—	—	27	32	77	39	18	88	15.6
67	54 F	PBC	—	—	5	42	497	39	12	67	20.7
68	31 F	CAH	—	—	22	208	125	31	21	71	21.5
69	50 M	CAH	—	—	11	52	86	39	15	74	35.6
70	41 M	CC	—	—	46	44	91	34	16	92	45.1

* CC, cryptogenic cirrhosis; PBC, primary biliary cirrhosis; CAH, chronic active hepatitis (HBsAg negative); Haem, haemochromatosis; Halothane, cirrhosis following halothane hepatitis; Septal, incomplete septal fibrosis.

+ reference range in parenthesis; AST, aspartate transaminase; ALP, alkaline phosphatase; PT, prothrombin time.

Bilirubin: $\mu\text{mol/l} \times 0.585 = \text{mg}/100 \text{ ml}$. ALP: $\text{U/l} \times 0.141 = \text{KAu}/100 \text{ ml}$. Albumin: $\text{g/l} \times 0.1 = \text{g}/100 \text{ ml}$.

Creatinine: $\mu\text{mol/l} \times 0.0113 = \text{mg}/100 \text{ ml}$.

The liver damage in the present four patients almost certainly resulted from perhexiline. None of the patients consumed excessive quantities of alcohol nor took other, potentially hepatotoxic drugs. Other manifestations of perhexiline toxicity were present; two patients showed disturbed balance (TB, DW), three showed significant weight loss (TB, DW, AG), three had peripheral neuropathy (TB, DW, AG) and one a proximal myopathy (DW). The liver lesions were similar to those already described following perhexiline and no other cause for the liver disease was found. Withdrawal of the drug resulted in a prompt improvement in the clinical condition and some biochemical tests in two patients; the remaining two patients deteriorated despite drug withdrawal, a course already well recognised after perhexiline liver injury.^{12 13 15 17 18 30}

Severe hepatotoxicity only occurs in a percentage of perhexiline treated patients. In the present study all four patients with perhexiline liver injury showed diminished drug elimination ability as measured by debrisoquine hydroxylation. In three of the four patients the metabolic ratio exceeded 12.6 indicating the PM phenotype. In the control group of 70 patients with chronic liver disease the proportion of patients with the PM phenotype was similar to that in the healthy population²² and there was no correlation between oxidation capacity and standard liver function tests. Thus the impairment of drug oxidation ability in the perhexiline damaged patients can not be explained simply on the basis of impaired hepatocellular function.

A clear association therefore exists between perhexiline liver injury and diminished drug oxidation capacity. As a result of impaired drug oxidation, perhexiline would be expected to accumulate¹⁹ and this might explain the toxic sequelae. The actual mechanism of the toxic reaction is unknown, but drug induced disturbances of phospholipid metabolism have been implicated.¹²

One of the four patients studied had a metabolic ratio of 2.6 which indicates a substantial metabolic impairment, but not the PM phenotype. Thus although drug oxidation status may be a major determinant of both therapeutic and toxic drug responses, other factors must also be important; HLA-B8 might be one such factor.⁴²

Perhexiline maleate is a useful agent in the management of intractable angina. Nevertheless the severe toxic side effects have limited its use. While routine assessment of oxidation status would allow more selective use of the drug this facility is not generally available. Thus careful monitoring of liver function is required in all patients prescribed perhexiline and prompt withdrawal indicated if liver

function tests become persistently abnormal on therapeutic doses.

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