Effect of liver disease on dextromethorphan oxidation capacity and phenotype: a study in 107 patients

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- 1 The *O*-demethylation of dextromethorphan to dextrorphan exhibits a genetically-controlled polymorphism, co-segregating with that of debrisoquine hydroxylation. Dextromethorphan has been proposed as a test compound to assess drug oxidation polymorphism.
- 2 We studied the effects of liver disease of varying severity on dextromethorphan oxidation capacity. Phenotyping was performed using the urinary dextromethorphan/dextrorphan metabolic ratio after oral administration of 40 mg dextromethorphan hydrobromide in 56 patients with cirrhosis and in 51 patients with moderately severe liver disease.
- 3 Dextromethorphan oxidation capacity was impaired in cirrhotic patients and, to lesser extent, in non cirrhotic patients, as compared with 103 control subjects.
- 4 The impairment in dextromethorphan oxidation induced by liver disease, was however, much less than that caused by the genetic deficiency. As a result, the prevalence of the poor metabolizer phenotype remained in the same range in patients with cirrhosis (1.8%) and with moderately severe disease (2.0%) as in controls (3.9%).
- 5 This observation shows that, although liver disease causes some impairment of dextromethorphan *O*-demethylation, this impairment is not sufficient to modify the assignment of phenotypes.

Keywords dextromethorphan oxidation capacity oxidation phenotyping liver disease

Introduction

Dextromethorphan is an effective compound which has been used in various cough-cold preparations for more than 20 years. Despite its structural similarity to opioids, this drug is considered as non-addictive and devoid of serious side-effects (Jaffe & Martin, 1985). Dextromethorphan elimination depends mainly on extensive hepatic oxidative metabolism (Pfaff *et al.*, 1983). The drug is mostly *O*-demethylated to dextrorphan and, to a much lesser extent, *N*-demethylated to methoxymorphinan. A small fraction of dextrorphan is further oxidized to hydroxymorphinan. These metabolites are then partially conjugated with sulphate and glucuronic

acid. After oral administration, more than 85% of the dose is excreted in urine within 24 h as free and conjugated metabolites and, as a very small proportion, unmetabolized dextromethorphan (Pfaff *et al.*, 1983). *O*-demethylation, the limiting step in dextromethorphan metabolism and elimination, is subject to a genetically-controlled polymorphism related to that of debrisoquine 4-hydroxylation (Küpfer *et al.*, 1984; Schmid *et al.*, 1985; Larrey *et al.*, 1987). Two phenotypes have been identified: most subjects are 'extensive metabolizers' (EM) whereas a minority of subjects, 3 to 10% of European and North American Caucasians, are 'poor

metabolizers' (PM) (Mahgoub *et al.*, 1977; Küpfer & Preisig, 1983; Jacqz *et al.*, 1986). The cytochrome P-450 isozyme mainly responsible for debrisoquine/dextromethorphan oxidation has been purified recently and characterized in several laboratories (Larrey *et al.*, 1984; Gut *et al.*, 1984; Distlerath *et al.*, 1985). Recent data show that the genetic deficiency in this oxidative pathway is probably caused by the complete (or almost complete) absence of this cytochrome P-450 isozyme in the liver of poor metabolizers (Gonzalez *et al.*, 1988; Zanger *et al.*, 1988). More than twenty drugs have been identified as being oxidized by this cytochrome P-450 isozyme including β -adrenoceptor blockers, tricyclic antidepressants, perhexiline and several anti-arrhythmic agents (Küpfer & Preisig, 1983; Jacqz *et al.*, 1986). These drugs display an oxidation polymorphism co-segregating with that of debrisoquine.

Dextromethorphan is used increasingly as a substitute for debrisoquine, to assess this oxidation genetic polymorphism. Indeed, dextromethorphan has the advantages over debrisoquine of being available worldwide and of being a safer drug (Schmid *et al.*, 1985; Larrey *et al.*, 1987).

In addition to genetic factors, drug oxidation is also dependent on the presence or absence of disease states, particularly liver disease (Vesell, 1979). Liver disease can markedly decrease cytochrome P-450 concentration and mono-oxygenase activities within the liver (Larrey & Branch, 1983). Liver disease can also interfere with drug absorption and distribution or modify hepatic haemodynamics (Larrey & Branch, 1983). These changes can seriously impair the ability of the liver to metabolize and eliminate some drugs. The extent of these effects vary not only with the type and severity of liver injury, but also, for a given liver injury, from one drug to another (Larrey & Branch, 1983). Furthermore, recent data suggest that the same liver disease may influence the activity of different cytochrome P-450 isozymes to a different extent (Larrey & Branch, 1983; Teunissen *et al.*, 1984).

The effects of liver disease on debrisoquine oxidation have not been investigated systematically and there have been conflicting findings from *in vitro* and *in vivo* studies. *In vitro*, debrisoquine 4-hydroxylation was found to be markedly decreased in liver samples from patients with histological evidence of liver disease (Kahn *et al.*, 1982). *In vivo*, however, debrisoquine oxidation phenotype was not significantly influenced by alcoholic and several non alcoholic liver diseases (Lanthier *et al.*, 1984).

Since dextromethorphan is being used as test

compound for the assessment of oxidation capacity, it is important to determine the influence of liver disease on its metabolism. The variations mentioned above make it difficult to extrapolate data observed for debrisoquine to dextromethorphan.

The aim of this study was to assess the effects of liver diseases of varying severity on dextromethorphan oxidation.

Methods

Patients

Subjects of the study comprised 107 patients with liver disease. Patients were classified into two groups according to the severity of liver injury. The criterion used for inclusion in the group with severe disease was the presence of cirrhosis. This group included 56 patients (41 males and 15 females), 20 to 82 years old (mean $\pm$ s.d., 53 ± 12). The diagnosis of cirrhosis was confirmed by histological examination in 54 patients, or by the presence of spider angiomas, oesophageal varices and mild ascites in the two remaining patients. The causes of cirrhosis were: alcohol abuse (31 cases), infection by hepatitis B virus (9 cases) or hepatitis non A non B virus (4 cases), auto-immunity (4 cases), Wilson's disease (one case), secondary biliary cirrhosis (one case); the origin was unknown in 6 cases. The criteria used for inclusion in the group with moderately severe liver disease were the absence of cirrhosis, the presence of only moderately severe histological lesions when a liver biopsy had been required for the diagnosis, and the absence of marked hepatic failure as judged by clinical examination and biological tests (prothrombin time $\geq 60\%$ of normal and serum albumin ≥ 32 g l⁻¹). This group included 51 patients (34 males and 17 females), 23 to 69 years old (mean $\pm$ s.d., 45 ± 13). Histological examination was performed in 44 of them. The group was made up of patients with alcohol-induced steatosis, alone or associated with mild or moderate acute alcoholic hepatitis and/or mild or moderate fibrosis (22 cases), viral or auto-immune chronic active hepatitis (15 cases), viral acute hepatitis (4 cases), granulomatous hepatitis (3 cases), early stage primary biliary cirrhosis (2 cases), Budd-Chiari syndrome (2 cases), polycystic disease of the liver (1 case), cholangiocarcinoma (1 case) and benign recurrent cholestasis (1 case). Pertinent clinical and biological data for each patient at the time of the study are indicated in Tables 1 and 2.

We excluded from the study, patients with serum creatinines above 150 μ mol l⁻¹, patients

Table 1 Clinical data and dextromethorphan metabolic ratio in patients with cirrhosis

<i>Patients</i>	<i>Age/Sex (years)</i>	<i>Cause of cirrhosis*</i>	<i>Serum ALT** (i.u.) (10–40)</i>	<i>Serum AST** (i.u.) (10–40)</i>	<i>Serum AP** (i.u.) (25–130)</i>	<i>Serum bilirubin ($\mu\text{mol l}^{-1}$) (< 15)</i>	<i>Serum albumin (g l⁻¹) (35–50)</i>	<i>Prothrombin time (% of normal) (70–100)</i>	<i>Dextromethorphan metabolic ratio</i>
1	39/M	Alcohol	14	39	61	29	34	40	0.0015
2	64/F	Autoimmunity	116	143	170	13	26	70	0.0029
3	51/F	Alcohol	29	59	149	55	35	52	0.0030
4	44/M	Alcohol	42	76	134	18	26	51	0.0034
5	62/F	Unknown	29	83	245	9	25	53	0.0041
6	52/M	HBV	22	41	93	14	36	40	0.0044
7	62/F	Autoimmunity	24	37	119	18	27	55	0.0048
8	46/M	Alcohol	31	121	322	84	26	58	0.0048
9	82/F	Unknown	61	55	104	11	36	58	0.0052
10	51/M	Alcohol	30	57	164	62	19	48	0.0053
11	53/M	Alcohol	20	37	89	14	40	71	0.0055
12	65/M	NA NB	203	252	90	18	43	83	0.0063
13	41/M	HBV	57	71	94	56	25	25	0.0086
14	61/M	Alcohol	35	99	65	78	27	44	0.0090
15	42/M	Alcohol	38	100	124	27	34	64	0.0097
16	40/M	Alcohol	49	96	118	41	49	68	0.0109
17	55/M	Alcohol	56	78	660	34	28	84	0.0113
18	57/M	HBV	178	162	151	14	42	52	0.0115
19	54/M	HBV	115	140	179	47	26	42	0.0134
20	21/M	Wilson	71	82	182	30	32	31	0.0147
21	36/M	HBV	160	160	169	29	24	61	0.0148
22	44/M	Alcohol	54	58	111	57	40	39	0.0150
23	20/F	Autoimmunity	23	23	55	13	42	48	0.0202
24	71/F	Alcohol	25	29	135	15	43	62	0.0212
25	50/M	Alcohol	21	42	395	59	40	26	0.0214
26	66/F	Autoimmunity	241	265	241	25	33	70	0.0226
27	42/M	Alcohol	35	42	97	26	40	68	0.0229
28	39/M	HBV	85	90	139	15	35	75	0.0250
29	67/M	Unknown	19	20	226	20	39	100	0.0259
30	44/M	Alcohol	51	170	222	86	38	62	0.0270
31	55/F	Alcohol	49	96	124	45	47	59	0.0288
32	56/M	Alcohol	20	52	65	17	33	56	0.0325
33	46/F	Alcohol	170	446	352	164	38	75	0.0350
34	47/M	NA NB	95	112	124	37	30	35	0.0359
35	48/F	Alcohol	40	40	130	40	29	66	0.0365
36	51/M	HBV	67	407	269	29	32	49	0.0367
37	60/M	HBV	131	146	160	21	41	85	0.0368
38	75/M	Unknown	36	54	171	14	25	60	0.0401
39	67/F	NA NB	53	70	145	11	43	76	0.0405
40	56/M	Alcohol	26	50	218	48	30	38	0.0660
41	41/M	Alcohol	19	30	130	18	45	92	0.0673
42	42/F	Alcohol	11	33	96	41	31	38	0.0683
43	52/M	SBC	33	38	107	11	41	70	0.0688
44	47/M	Alcohol	60	68	127	12	48	68	0.0886
45	47/F	Unknown	84	80	672	19	36	76	0.1037
46	57/M	NA NB	68	81	51	20	27	58	0.1053
47	64/M	Alcohol	15	25	79	20	33	51	0.1107
48	67/M	Unknown	22	25	109	51	33	61	0.1310
49	56/M	Alcohol	65	124	265	48	36	70	0.1474
50	59/M	Alcohol	30	52	87	23	30	48	0.1836
51	56/M	HBV	60	197	132	141	22	28	0.1862
52	55/M	Alcohol	39	39	125	13	43	63	0.1920
53	47/F	Alcohol	47	64	376	22	26	52	0.1950
54	54/M	Alcohol	40	121	106	19	28	60	0.2373
55	61/M	Alcohol	47	55	136	37	29	51	0.2440
56	59/M	Alcohol	46	72	27	40	25	54	0.9520

* HBV, hepatitis B virus; NA NB, hepatitis non A non B virus; SBC, secondary biliary cirrhosis.

** ALT, alanine aminotransferase; AST, aspartate aminotransferase; AP, alkaline phosphatase; reference range in parenthesis.

Table 2 Clinical data and dextromethorphan metabolic ratio in patients with moderately severe liver disease

<i>Patients</i>	<i>Age/Sex (years)</i>	<i>Type of liver disease*</i>	<i>Serum ALT** (i.u.) (10–40)</i>	<i>Serum AST** (i.u.) (10–40)</i>	<i>Serum AP** (i.u.) (25–130)</i>	<i>Serum bilirubin ($\mu\text{mol l}^{-1}$) (< 15)</i>	<i>Serum albumin (g l⁻¹) (35–50)</i>	<i>Prothrombin time (% of normal) (70–100)</i>	<i>Dextromethorphan metabolic ratio</i>
1	35/M	AH, NA NB	262	54	74	28	45	90	0.0014
2	60/M	AS, F	51	56	75	5	38	96	0.0016
3	24/M	CAH, HBV	26	19	46	18	43	84	0.0030
4	34/M	CAH, HBV	548	284	143	10	42	76	0.0034
5	66/M	AS	171	244	69	6	38	80	0.0035
6	50/M	AS	41	60	85	9	49	89	0.0036
7	56/F	CAC	1010	427	1060	48	45	91	0.0039
8	49/M	AS	170	48	970	9	47	100	0.0039
9	69/F	CAH, AI	29	36	453	7	33	79	0.0039
10	27/M	AH, HBV	573	436	224	72	43	75	0.0044
11	69/F	GH	282	132	63	8	42	82	0.0052
12	49/M	AS, AAH	266	162	106	21	53	88	0.0054
13	37/M	AS	108	198	104	8	44	100	0.0066
14	29/M	AS, F	97	180	50	14	37	65	0.0073
15	36/F	AS	32	91	36	17	37	82	0.0079
16	52/F	CAH, AI	51	79	130	46	36	65	0.0080
17	46/M	AS, AAH, F	105	230	51	7	43	70	0.0098
18	43/M	AS, F	50	45	85	4	47	100	0.0099
19	32/M	AS	114	153	120	21	44	91	0.0099
20	35/M	AS, F	34	56	118	11	47	100	0.0101
21	23/F	AH, HAV	1300	269	166	73	39	96	0.0101
22	27/M	AS	111	170	75	16	40	90	0.0122
23	32/M	CAH, HBV	128	83	67	15	36	85	0.0128
24	38/F	CAH, NA NB	49	53	90	7	42	87	0.0141
25	40/M	BRC	43	63	509	473	32	60	0.0143
26	44/M	CAH, NA NB	137	59	114	33	51	82	0.0145
27	43/M	CAH, HBV	402	211	122	30	50	93	0.0146
28	23/M	CAH, HBV	362	137	94	8	40	80	0.0154
29	43/F	CAH, HBV	128	90	63	2	41	65	0.0156
30	44/M	AS, F	91	108	103	15	48	100	0.0173
31	53/M	AH, NA NB	146	66	65	10	47	69	0.0191
32	62/M	BCS	32	55	151	38	38	63	0.0262
33	52/F	CAH, AI	236	88	61	7	40	66	0.0268
34	64/M	AS, F	82	212	302	87	36	60	0.0270
35	66/F	CAH, AI	154	134	62	16	44	71	0.0270
36	42/M	AS	23	21	74	10	34	75	0.0273
37	51/F	AS, AAH, F	22	87	102	18	32	62	0.0285
38	58/M	AS, AAH	102	232	44	32	40	79	0.0290
39	23/M	CAH, HBV	166	70	91	6	40	65	0.0332
40	38/M	BCS	49	52	298	17	41	70	0.0510
41	58/M	AS, F	16	26	76	13	43	100	0.0548
42	53/F	PBC	32	43	483	14	44	74	0.0571
43	27/M	GH	101	39	195	15	42	80	0.0740
44	65/F	GH	27	31	118	10	46	72	0.0858
45	43/F	AS, AAH, F	16	51	55	6	40	84	0.0985
46	60/F	PCDL	15	16	88	11	41	80	0.1220
47	42/M	AS	70	84	98	22	38	100	0.1412
48	39/M	AS	45	29	89	14	52	83	0.1479
49	50/F	PBC	42	62	848	12	35	60	0.1700
50	50/F	CAH, NA NB	155	269	98	24	39	100	0.2773
51	34/M	CAH, HBV	168	51	66	21	42	70	0.7830

* AH, acute hepatitis; CAH, chronic active hepatitis; HBV, hepatitis B virus; NA NB, hepatitis non A non B virus; HAV, hepatitis A virus; AI, auto-immune; AS, alcoholic steatosis; AAH, mild or moderate acute alcoholic hepatitis; F, mild or moderate fibrosis; CAC, cholangiocarcinoma; BCS, Budd-Chiari syndrome; BRC, benign recurrent cholestasis; PCDL, polycystic disease of the liver; PBC, early stage primary biliary cirrhosis.

** ALT, alanine aminotransferase; AST, aspartate aminotransferase; AP, alkaline phosphatase; normal range in parenthesis.

taking drugs likely to interfere with dextromethorphan oxidation or alcoholic patients who had not abstained from alcohol within the next week before the test. All patients gave their informed consent to the study which was approved by the local Ethics Committee.

Dextromethorphan oxidation capacity and phenotyping

Drug oxidation capacity was assessed as described recently (Larrey *et al.*, 1987). The subjects were given two capsules of dextromethorphan hydrobromide orally (20 mg/capsule kindly supplied by Hoffmann-LaRoche Laboratory) at 22.00 h and urine was collected for 10 h thereafter. The phenotype was assigned using the metabolic ratio (MR) calculated as

$$\text{MR} = \frac{\text{urinary output of unchanged dextromethorphan (0-10 h)}}{\text{urinary output of dextrorphan (0-10 h)}}$$

Dextromethorphan and dextrorphan were measured in urine by h.p.l.c. assay as reported previously (Larrey *et al.*, 1987). The poor metabolizer phenotype is characterised by a metabolic ratio above 0.3 (or log MR above -0.5) (Schmid *et al.*, 1985; Larrey *et al.*, 1987).

The results observed in patients with liver disease were compared with those found during the same period in our laboratory in 103 healthy subjects used as a control population (Larrey *et al.*, 1987).

Statistical analysis

Fisher's exact test was used to compare the prevalence of each phenotype between the different groups. One way analysis of variance was used to compare the mean values of dextromethorphan and dextrorphan urinary outputs and the mean log metabolic ratio between different subgroups of patients and control subjects with the EM phenotype.

Results

Individual dextromethorphan metabolic ratios found in patients with cirrhosis or with moderately severe liver disease are shown in Tables 1 and 2, respectively. In the group of cirrhotic patients, 55 had a metabolic ratio below 0.3 and were classified as extensive metabolizers (98.2%), whereas one patient with a metabolic ratio above 0.3 had the PM phenotype (frequency of 1.8% with a 95% confidence interval of 0 to 5.2%) (Table 3). In the group of patients with moder-

ately severe liver disease, 50 were classified as EMs (98%) and one as a PM (frequency of 2% with a 95% confidence interval of 0 to 5.8%) (Table 3). The mean values of dextromethorphan and dextrorphan urinary outputs, and the mean metabolic ratio observed in EMs and PMs from both groups are shown in Table 3.

The results found in patients were compared with those observed in 103 healthy control subjects (Larrey *et al.*, 1987) (Table 3). In patients with liver disease (cirrhotic and non cirrhotic) classified as having the EM phenotype, the mean dextrorphan urinary output was lower and the mean dextromethorphan urinary output was slightly higher, than in control subjects having the EM phenotype (Table 3). These changes tended to be more marked in patients with cirrhosis than in patients with moderately severe liver disease (without reaching statistical significance). The mean metabolic ratio was two times higher in non cirrhotic patients, and three times higher in cirrhotic patients, than in control subjects (Table 3). Consistently, the frequency distribution histograms of log metabolic ratio were shifted to the right in both groups of patients as compared with the group of control subjects (Figure 1). The increase in the metabolic ratio of patients with liver diseases, however, was not sufficient to affect the prevalence of phenotypes which remained similar in patients and in control subjects (Table 3).

We examined the data to see whether these results may have been influenced by the cause of liver disease. Thus, data from the 53 patients with alcoholic liver injury (31 cirrhotic and 22 non cirrhotic patients) were compared with that from the 54 patients with non alcoholic liver injuries (25 cirrhotic and 26 non cirrhotic patients). There was no difference in the prevalence of the PM phenotype (2% *vs* 1.8%). Similarly, the 52 alcoholic EMs and the 53 non alcoholic EMs exhibited similar results (mean $\pm$ s.d.) in mean dextromethorphan urinary output (0.98 ± 1.29 *vs* 0.93 ± 0.90 $\mu\text{mol } 10 \text{ h}^{-1}$), in mean dextrorphan urinary output (33.7 ± 32.6 *vs* 36.1 ± 21.8 $\mu\text{mol } 10 \text{ h}^{-1}$) and in mean log metabolic ratio (-1.68 ± 0.59 *vs* -1.72 ± 0.53).

We found no significant correlation between the metabolic ratio and levels of serum aspartate aminotransferase, serum alkaline phosphatase serum bilirubin, serum albumin or prothrombin time.

Discussion

This study demonstrates that dextromethorphan oxidation capacity is impaired in patients with

Table 3 Comparison of dextromethorphan and dextrothorphan urinary output (0–10 h) and metabolic ratio in 103 healthy control subjects, in 56 patients with cirrhosis and in 51 patients with moderately severe liver disease. Results are expressed as means $\pm$ s.d. values are indicated between parentheses

Phenotype	Healthy control subjects		Patients with cirrhosis		Patients with moderately severe liver disease	
	Extensive metabolizers	Poor metabolizers	Extensive metabolizers	Poor metabolizers	Extensive metabolizers	Poor metabolizers
Number of subjects	99	4	55	1	50	1
Phenotype prevalence (%)	96.1	3.9	98.2	1.8	98.0	2.0
Dextromethorphan output ($\mu\text{mol } 10 \text{ h}^{-1}$)	0.71 ± 0.77 (0.45)	12.97 ± 5.91 (10.41)	1.00 ± 1.14 (0.59)	12.95	0.88 ± 1.06 (0.55)	12.46
Dextrothorphan output ($\mu\text{mol } 10 \text{ h}^{-1}$)	48.7 ± 20.9 (45.9)	8.7 ± 6.9 (8.4)	$32.1 \pm 27.9^*$ (23.8)	13.6	$37.7 \pm 26.9^*$ (31.9)	15.9
Dextromethorphan metabolic ratio (MR)	0.016 ± 0.017 (0.009)	2.409 ± 0.658 (1.973)	$0.052 \pm 0.065^{**}$ (0.025)	0.952	$0.035 \pm 0.053^{**}$ (0.014)	0.784
log MR	-1.99 ± 0.43 (-2.03)	$+0.22 \pm 0.50$ (+0.29)	$-1.61 \pm 0.57^{**}$ (-1.60)	-0.02	$-1.80 \pm 0.54^{**}$ (-1.85)	-0.11

*, **Results significantly different from those found in control subjects with EM phenotype. One way analysis of variance, * $P < 0.05$, ** $P < 0.01$.

Figure 1 Comparison of frequency distribution histograms of the dextromethorphan log metabolic ratio in 103 healthy control subjects, in 51 patients with moderately severe liver disease and in 56 patients with cirrhosis. □ extensive metabolisers, ▨ poor metabolisers.

cirrhosis or moderately severe liver disease as shown by the decrease in mean dextromethorphan urinary excretion, and the increase in mean unmetabolized dextromethorphan urinary excretion and in the mean metabolic ratio (Table 3). The impairment was more marked in patients with cirrhosis although this did not reach statistical significance. These data are consistent with

a previous *in vitro* study showing that debrisoquine 4-hydroxylation, which depends mainly on the same cytochrome P-450 isozyme as dextromethorphan *O*-demethylation, was decreased in liver samples from patients with liver disease (Kahn *et al.*, 1982).

The impairment in dextromethorphan oxidation induced by moderate or even severe liver diseases, however, is much less than that observed in genetically deficient subjects (Table 3). Indeed, despite its increase, the mean dextromethorphan metabolic ratio in cirrhotic patients was still 6 times lower than that corresponding to the anti-mode separating EMs and PMs. As a result, cirrhosis or moderate liver diseases ultimately have no significant consequence for the assignment of EM and PM phenotypes determined by this method. This observation is in agreement with a recent report showing that debrisoquine oxidation phenotype assessed from the metabolic ratio, was not affected by various liver diseases (Lanthier *et al.*, 1984).

We found no correlation between dextromethorphan oxidation polymorphism and the risk of developing alcoholic liver diseases since only one of the 53 alcoholic patients had the PM phenotype. Similarly, there was no significant relationship between the extent of dextromethorphan oxidation impairment and the alcoholic origin of liver diseases. These results are similar to those observed for debrisoquine oxidation (Lanthier *et al.*, 1984).

Finally, there was no correlation between the metabolic ratio and the results of standard liver biochemical tests, in particular serum albumin and prothrombin time which are frequently used to evaluate the severity of liver diseases. This illustrates that these standard tests have no value in predicting the effects of liver diseases on dextromethorphan oxidation capacity.

We conclude that dextromethorphan oxidation capacity is impaired in patients with cirrhosis and, to a lesser extent, in patients with moderately severe liver disease. This impairment, however, is not sufficient to interfere with the assignment of PM and EM phenotypes determined *in vivo* using the dextromethorphan metabolic ratio.

We wish to thank Professor J. P. Benhamou for allowing us to test patients from the Service d'Hépatologie at Hôpital Beaujon.

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(Received 8 December 1988,
accepted 31 March 1989)