Dextromethorphan phenotypes in paediatric patients with autoimmune hepatitis

Autoimmune hepatitis is characterised by the presence in sera of anti-smooth muscle antibody (SMA), or anti-liver kidney microsome antibody (LKMA) (Odièvre *et al.*, 1983). It was recently reported that anti-LKMA type 1 specifically recognizes a microsomal protein of M_r 48 kD in humans and M_r 50 kD in rats, further identified as cytochrome P450IID6 in man (Gueguen *et al.*, 1989). P450IID6 exhibits polymorphic activity under genetic control. Dextromethorphan (DEM) metabolism to dextrorphan (DOR), is a specific marker of P450IID6 activity (Kupfer *et al.*, 1984). Urinary metabolic ratios (DEM/DOR) are bimodally distributed, with an antimode of 0.3 between extensive (EM) and poor (PM) metabolizers (3 to 9% of the Caucasian population) (Jacqz-Aigrain *et al.*, 1988). Although subjects' PM for debrisoquine studied to date *in vitro* have been characterized by the absence of P450IID6 (antigen negative PM), it is clear from other gene defects that the PM phenotype could also result from mutations giving rise to an abnormal P450IID6 protein (putative antigen positive PM). The hypothesis that P450IID6 mutants can give rise to anti LKM1 auto antibodies is therefore worth testing. As a first step, we searched for a phenotypic predisposition to the appearance of the disease, and phenotyped 13 affected children and 31 control paediatric patients with dextromethorphan.

Children with autoimmune hepatitis were between 5 and 16 years old. Diagnostic criteria have been previously defined (Maggiore *et al.*, 1986). The type of antibody was identified by immunofluorescence at the onset of autoimmune hepatitis: one patient had anti-SMA, one had anti-cytosol antibody, and 10 had anti-LKMA. In immunoblot analysis of rat liver microsomes, six LKMA positive sera showed anti-50 kD antibody (associated with anti-66 kD in two cases) and four showed anti-66 kD reactivity alone (Codoner-Franch *et al.*, 1989). The delay between diagnosis and inclusion in the study was at least 6 months. None of the patients exhibited biochemical signs of liver change at the time of study. Concomitant drug therapy included prednisone (0.2 to 0.6 mg kg^{-1} every other day) and azathioprine (1.5 mg kg^{-1} daily), associated in one case with cyclosporin (6 mg kg^{-1} daily). Control paediatric patients (5 to 16 years old) were from the Department of Surgery (Professor Bensahel, Hôpital Robert-Debré). They were not taking any drug known to interfere with dextromethorphan metabolism. This study was approved by the Ethics Committee of the University Bichat-Beaujon, Paris. Parents gave informed consent.

On the day of the study, before going to bed, each child was asked to empty the bladder and to take one capsule of 20 mg dextromethorphan (Laboratoires Norgan, Paris, France). Urine

Table 1 DEM and DOR elimination and DEM/DOR ratios were not statistically different between the two groups of EMs. The results are expressed as mean ± s.e. mean

	DEM ($\mu mol\ 8\ h^{-1}$)	*DOR* ($\mu mol\ 8\ h^{-1}$)	*DEM/DOR*
Autoimmune hepatitis			
EM $n = 12$			
Anti 50 kD ($n = 6$)	0.06 ± 0.01	10.87 ± 2.7	0.006 ± 0.002
Anti 66 kD ($n = 4$)	0.08 ± 0.06	13.48 ± 4.4	0.016 ± 0.02
Anti cytosol ($n = 1$)	0.09	13.37	0.007
Anti SMA ($n = 1$)	0.09	6.12	0.015
Mean	0.07 ± 0.01	11.64 ± 1.8	0.016 ± 0.006
PM $n = 1$			
Anti cytosol	0.17	0.03	6.18
Control paediatric population			
EM $n = 29$	0.19 ± 0.05	10.5 ± 0.8	0.019 ± 0.005
PM $n = 2$	3.68	0.68	5.4
	2.75	0.81	3.4

was collected for the following 8 h (overnight), and aliquots were kept frozen until analysis (−20° C). Concentrations of dextromethorphan and dextrorphan were measured by high-performance liquid chromatography with fluorescence detection (Jacqz-Aigrain *et al.*, 1989), and phenotypes were determined based on the metabolic ratio. An antimode of 0.3 was used to separate EM and PM subjects (Kupfer *et al.*, 1984).

Both EM and PM subjects were identified in the group of children with autoimmune hepatitis, and both the frequency and the metabolic ratios of EMs were similar to those of the control paediatric group (Table 1). Children with anti 50-kD antibody were all EM. Our results suggest that the PM phenotype is not a risk factor for induction and progression of this specific disease.

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(Received 1 November 1989,
accepted 5 March 1990

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