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HEPATIC ENZYME INDUCTION AND ITS RELATIONSHIP TO URINARY D-GLUCARIC ACID EXCRETION IN MAN

The previously reported study of the effects of phenobarbitone on hepatic drug-metabolizing enzymes and urinary D-glucaric acid excretion in man (Lecamwasam, Franklin & Turner, 1975) has been extended to include twenty-eight patients with Hodgkin's disease and their clinical data are summarized in Table 1. The mean age and weight of the two groups of patients were not significantly different. Patients in both groups had no clinical evidence of hepatocellular dysfunction, although three patients in the phenobarbitone untreated group had repeatedly elevated serum alkaline phosphatase activity. Drug-metabolizing enzyme activities of these three patients as well as the smokers were in the same range as others in their respective groups.

In the untreated group of patients, there was no significant correlation between any of the hepatic drug-metabolizing enzymes (hexobarbitone oxi-

dase activity, HBO; microsomal cytochrome P-450 content, Cyt. P-450; *p*-nitroreductase activity, PNR; 1-leucyl- β -naphthylamide splitting enzyme, LNSE; UDP-glucuronyl transferase activity, UDPGT), or microsomal protein content (MP) and urinary D-glucaric acid (D-GA) excretion (Table 2). Recent studies in untreated volunteers have demonstrated the absence of a significant correlation between urinary D-glucaric acid and other indirect indices of drug metabolism (Smith & Rawlins, 1974) except between urinary D-glucaric acid excretion and the elimination constant K_2 of aminopyrine (Hildebrandt, Roots, Speck, Saalfrank & Kewitz, 1975). However, these authors have concluded that in untreated subjects such a significant correlation cannot be expected.

Phenobarbitone treatment resulted in a significant increase in hexobarbitone oxidase activity, microsomal cytochrome P-450 content,

Table 1 Clinical data of patients

Patient group	Age (years)	Weight (kg)	Cigarettes > 15/day	Regular alcohol	Abnormal L.F.T.	Abnormal liver histology
Untreated						
Male = 9	33.9	66.7				
Female = 7	± 3.5	± 3.2	4	1	3	1
Treated						
Male = 6	32.9	65.7				
Female = 6	± 3.4	± 3.2	3	Nil	Nil	1

L.F.T. Liver function tests.

Treatment Phenobarbitone (30 mg 8 hourly) for 7 to 21 days (Mean 13)

UDP glucuronyl transferase activity and the microsomal protein content. There was no difference in the activities of *p*-nitroreductase and l-leucyl- β -naphthylamide splitting enzyme between the untreated and the treated patients. Comparison of the pre- and post-phenobarbitone D-glucaric acid excretions shows that pheno-

barbitone treatment also significantly increased the D-glucaric acid excretion (Table 3). However, the only directly measured induced index that had a significant correlation with post-phenobarbitone urinary D-glucaric acid excretion was the microsomal cytochrome P-450 content ($r = 0.62$; $P < 0.05$). Moreover, there was no significant

Table 2 Matrix of the correlation coefficients (r) between urinary D-glucaric acid and drug-metabolizing enzyme activities in phenobarbitone untreated patients

	D-GA	Cyt. P-450	HBO	PNR	LNSE	UDPGT	MP
D-GA	—	0.04 (16)	-0.01 (11)	0.12 (10)	-0.31 (16)	-0.28 (15)	-0.17 (16)
Cyt. P-450	—	—	0.26 (11)	0.49 (10)	0.11 (16)	-0.12 (15)	0.27 (16)
HBO	—	—	—	-0.10 (7)	0.04 (11)	0.51 (11)	0.22 (11)
PNR	—	—	—	—	0.00 (10)	-0.51 (9)	0.10 (10)
LNSE	—	—	—	—	—	0.31 (15)	0.47 (16)
UDPGT	—	—	—	—	—	—	0.37 (15)
MP	—	—	—	—	—	—	—

The numbers in parentheses indicate the number of pairs of observation

D-GA D-glucaric acid; Cyt. P-450 cytochrome P-450; HBO hexobarbitone oxidase; PNR *p*-nitroreductase; LNSE l-leucyl- β -naphthylamide splitting enzyme; UDPGT UDP-glucuronyl transferase; MP microsomal protein.

Table 3 Effect of phenobarbitone (PB) on the indices of drug metabolism

Patient group	Enzyme activities						D-GA	
	HBO	Cyt P-450	PNR	LNSE	UDPGT	MP	Pre-PB	Post-PB
Untreated								
Male = 9	2.43	6.79	0.69	45.8	1.082	31.0	15.5	
Female = 7	± 0.20 (11)	± 0.29 (16)	± 0.05 (10)	± 3.9 (16)	± 0.047 (15)	± 1.4 (16)	± 2.9 (16)	
Treated								
Male = 6	4.24	11.83*	0.74	46.9	1.303	38.6	15.6	51.6*
Female = 6	± 0.21 (11)	± 0.81 (12)	± 0.16 (9)	± 2.4 (12)	± 0.080 (12)	± 1.2 (12)	± 3.3 (12)	± 7.4 (12)
<i>P</i>	<0.001	<0.001	NS	NS	<0.02 >0.01	<0.001		<0.001

* Correlation coefficient r between Post-PB D-GA and Cyt. P-450 = 0.62; $P < 0.05$

The values given are the means $\pm$ s.e. mean

The numbers of patients in which the estimations were carried out are given in parentheses

P = Significance level of unpaired t -test for microsomal enzyme group means comparison and paired t -test for pre-PB and post-PB D-GA comparison

NS = Not significant ($P > 0.05$)

The abbreviations for enzyme activity are explained in Table 2

All activities are expressed as $\mu\text{mol g}^{-1}$ liver h^{-1} except cyt P-450 (nmol g^{-1} liver), MP (mg g^{-1} liver) and D-GA ($\mu\text{mol 24 h}^{-1}$)

Table 4 Matrix of the correlation coefficients (*r*) between the induced indices of drug-metabolism in phenobarbitone treated patients

		Cyt.			
	D-GA	P-450	HBO	UDPGT	MP
D-GA	—	0.62* (12)	0.27 (11)	0.37 (12)	-0.01 (12)
Cyt. P-450	—	—	0.31 (11)	0.49 (12)	-0.28 (12)
HBO	—	—	—	0.43 (11)	0.05 (11)
UDPGT	—	—	—	—	-0.21 (12)
MP	—	—	—	—	—

* Significance level $P < 0.05$

The numbers in parentheses indicate the number of pairs of observations

correlation between cytochrome P-450 content and other induced indices of microsomal drug metabolism (Table 4).

This study shows, in man as in guinea-pigs (Hunter, Maxwell, Stewart & Williams, 1973), there is a significant correlation between urinary D-glucuric acid excretion and microsomal cytochrome P-450 content following enzyme induction. However, enzyme induction depends on a multitude of factors including the dose and physicochemical properties of the inducing drug, duration of therapy and clinical condition of the patient. Furthermore, the glucuronic acid pathway involves enzymes other than those involved in drug metabolism. Hence, care must be taken not to interpret a relationship of association as one of cause and effect.

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