Stimulation of drug metabolism by centrally active drugs

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Exposure to drugs such as phenobarbitone may produce tolerance, both to barbiturates and to other subsequently administered drugs, as a result of induction of liver microsomal enzymes involved in drug metabolism. This can be demonstrated in animal studies from *in vitro* measurement of liver microsomal enzyme activity and in man may be inferred from changes in the plasma half-life of test drugs such as antipyrine. It is likely that the degree of induction will be maximal when large doses of drug have been administered chronically. The antipyrine half-life values that we have obtained in barbiturate dependent patients (4·3±0·2 h, mean±S.E.M.) are lower than those reported to occur following acute phenobarbitone treatment (8·0±0·1 h; Vessel & Page, 1969) or in farmworkers exposed to insecticides (7·7±0·1 h; Kolmodin *et al.*, 1969). Our studies on antipyrine metabolism in barbiturate dependent patients also indicates that following the withdrawal of a drug, metabolizing capacity gradually returns to normal.

As there is a lack of information on the effect on drug metabolism of many centrally active drugs we have extended our studies on the effects of chronic barbiturate administration (Stevenson & Turnbull, 1968) to studies on animals treated chronically with drugs as detailed in Table 1. With the exception of ethanol, amphetamine and morphine, which had no effect, these drugs produced an appreciable increase in the activity of the liver microsomal enzymes involved in barbiturate oxidation. The elevation with Mandrax was particularly marked (Table 1). Since these drugs are widely prescribed it is obviously of some importance to study their influence on drug metabolism in man. Investigations are currently in progress, using the antipyrine half-life assay, to ascertain the extent of this effect.

TABLE 1. *Effect of chronic treatment with centrally active drugs on the ability of rat liver microsomal preparations to oxidize barbiturate* in vitro

	Dose (mg/kg)/day							Barbiturate oxidation *in vitro*
Week	1	2	3	4	5	6	Route	(ratio to control)
Amphetamine	2·5	7·5	15	25	—	—	Drinking water	0·77
Barbitone	100	200	300	400	—	—	Drinking water	6·12
Chlordiazepoxide	10	30	50	100	—	—	Food	5·80
Meprobamate	250	750	1500	2000	—	—	Food	4·80
Methaqualone/ diphenhydramine (10:1, Mandrax)	100	300	600	600	—	—	Food	8·95
Methyprylon	100	300	500	700	—	—	Drinking water	4·70
Morphine	2–4	8–30	60–120	160–240	—	—	Drinking water and i.p. injection	1·04
Nitrazepam	10	40	100	200	—	—	Food	2·63
	Concentration in drinking water (% v/v)							
Ethanol	5	10	12·5	15	17·5	20		0·99

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