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Drug-metabolizing capacity in states of drug dependence and withdrawal

B. BALLINGER, M. BROWNING, K. O'MALLEY AND I. H. STEVENSON

Departments of Psychiatry, Clinical Chemistry and Pharmacology and Therapeutics, University of Dundee

Summary

1. Drug-metabolizing capacity was assessed in 8 barbiturate-dependent and in 3 Mandrax-dependent patients using, as indices, plasma antipyrine half-life and in some cases urinary output of 6β-hydroxycortisol. For comparison, antipyrine half-life was also measured in volunteers before and after a period of taking hypnotic doses of these agents.

2. Both indices indicated a very high drug-metabolizing capacity in the dependent subjects on admission, the antipyrine half-life value in the barbiturate patients being the shortest reported to date for any drug-exposed group. The urinary output of 6β-hydroxycortisol was approximately three times that in a control population.

3. This induction of drug-metabolizing capacity presumably contributed to the marked drug tolerance observed in the dependent patients.

4. It appeared that drug-metabolizing capacity eventually returned to normal levels after withdrawal of the barbiturate.

5. It is concluded that the abnormal drug-metabolizing capacity of dependent patients must be taken into account in assessing dose requirements for other drugs.

Introduction

The induction of hepatic microsomal drug-metabolizing enzymes in man following treatment with barbiturates and some other hypnotics, is well documented (Conney, 1967 ; Prescott, 1969). The resulting increase in rate of metabolism may account in part for the tolerance which develops to such agents with prolonged use. The most marked induction effects may be expected following chronic exposure to high doses of these drugs as occurs, for example, in states of barbiturate dependence. Stevenson & Turnbull (1968) reported marked induction of drug-metabolizing enzymes in barbiturate-dependent rats and observed, surprisingly, sub-normal levels of enzyme activity at some time after barbiturate withdrawal. This paper reports the results from a comparable study in man on drug-metabolizing capacity in patients dependent on and withdrawn from barbiturates or Mandrax (methaqualone 10 : diphenhydramine 1). In this investigation, plasma phenazone (antipyrine) half-life values and urinary output of 6β-hydroxycortisol (6β-OHF) have been used as indices of drug-metabolizing capacity. Antipyrine is protein bound to a very slight extent (Soberman, Brodie, Levy, Axelrod, Hollander & Steele, 1949) and its rate of elimination from the plasma is determined

by the rate at which it is oxidized in the liver. Since liver microsomal drug-metabolizing enzymes are relatively non-specific, the rate at which an individual metabolizes antipyrine may reflect his capacity to oxidize other drugs. Urinary output of 6β-OHF is used as an index since the 6β-hydroxylation of cortisol requires the same microsomal enzyme system as is involved in the oxidation of drugs (Kuntzman, Jacobson, Schneidman & Conney, 1964). Drugs which induce microsomal enzymes increase the rate of formation and urinary excretion of 6β-OHF.

Some of the results of this study have been published in a preliminary communication (Stevenson, O'Malley & Ballinger, 1970).

Methods

Patients

Patients who were included in the study fulfilled the following criteria:

(a) a history of taking barbiturates (8 patients) or Mandrax (3 patients) over a long period, the daily dose over the previous month being at least 400 mg of barbiturate or 600 mg of Mandrax;

(b) evidence of withdrawal symptoms or signs on stopping the hypnotic;

(c) no record of other drug taking during this period.

Details of the individual patients studied and two exceptions to (c) above are given in Table 1.

Treatment with hypnotic doses of barbiturate or Mandrax

For comparison, antipyrine half-life was measured in volunteers before and after exposure to amylobarbitone (Amytal, 200 mg) or Mandrax (275 or 550 mg) taken nightly for a three week period. Where subjects experienced side effects the lower dose of Mandrax was used.

TABLE 1. *Drug history and withdrawal symptoms of patients studied*

Patient	Age & sex		Drug and approx. duration of exposure (yr)		Approx. drug requirement on admission (mg/day)	Withdrawal symptoms
A*	41	F	Pentobarbitone	2	600–1,200	Insomnia, irritability, anxiety
B	55	F	Pentobarbitone	13	700	Tremor, vomiting, insomnia
			Amylobarbitone	1	180	
C	59	F	Amylobarbitone	1	1,000	Convulsions
D	57	M	Pentobarbitone	3	400+	Convulsions
E	41	M	Amylobarbitone	3	480	Anxiety, restlessness, tremor
			Pentobarbitone		200	
F	55	F	Pentobarbitone	7	200	Insomnia
			Amylobarbitone		240	
G	71	F	Amylobarbitone	5	600	Insomnia, irritability
H†	58	F	Amylobarbitone	20	600	Anxiety, vomiting, tremor
I	24	M	Mandrax	2	600	Not withdrawn on this occasion
J	40	F	Mandrax	2	1,500	Irritability, insomnia
K	33	F	Mandrax	3	600–2,500	Anxiety, irritability

* Meprobamate 200 mg twice daily for 1 month prior to start of study. † On thyroxine 0·1 mg/day throughout study.

Scheme of hypnotic withdrawal

After admission, patients were kept on full drug dose for the first three days, the dose then being reduced 10% per day for the following ten days. Antipyrine assays were carried out as follows:

I—day 2, full drug dose
II—day 8, 50% drug dose
III—day 20, 7 days drug free
IV—day 50, 37 days drug free.

Where drug therapy was required, patients were excluded at that point from the study. Urine samples were screened periodically for the presence of hypnotic after the withdrawal phase (Ballinger & Stewart, 1971).

Plasma antipyrine half-life

Antipyrine (18 mg/kg) was given in aqueous solution diluted with orange juice, the total volume being approximately 50 ml. Four plasma samples were taken into lithium heparin at approximately 3-hourly intervals thereafter. The unchanged antipyrine in plasma samples was estimated by the method of Brodie, Axelrod, Soberman & Levy (1949).

Urinary 6β-hydroxycortisol

For 6β-OHF, single 24 h urine collections were made on day 2 and estimations carried out by the method of Thrasher, Werk, Choi, Sholiton, Meyer & Olinger (1969). Results were expressed as a ratio to total 17-hydroxycorticosteroid (17-OHCS), estimated by the method of Few (1961).

Results

All of the patients studied had a history of prolonged exposure to barbiturates or Mandrax and evidence of dependence on these as indicated by the withdrawal symptoms listed (Table 1). The plasma antipyrine half-life values measured in the dependent patients on full drug dose are shown in Table 2 along with, for comparison, the values in a large control group (O'Malley, Crooks, Duke & Stevenson, 1971) and those found in volunteers before and after a 3-week period of taking hypnotic doses of amylobarbitone or Mandrax. It is evident that the

TABLE 2. *Plasma antipyrine half-life in hypnotic-exposed groups*

		No. of subjects		Plasma antipyrine half-life (h)
Control (no drugs)		61		12·0±3·5
Barbiturate-dependent		8		5·3±1·2 ($P<0·001$)
Mandrax-dependent		3		6·2±2·0 ($P<0·01$)
			Pre	Post
Amylobarbitone	Hypnotic dose for 3 weeks	9	12·3±3·9	8·7±2·1 ($P<0·05$)
Mandrax		14	14·8±4·6	10·8±3·2 ($P<0·005$)

Results are shown as means ± S.D. The antipyrine assays in the drug-dependent patients were carried out on day 2 of the study (i.e. patients on full drug dose). The levels of significance shown refer to differences between the means for dependent patients and for controls, and between those for dependent patients and subjects taking the hypnotic doses of the corresponding drug.

plasma antipyrine half-life is significantly shorter in the dependent patients than in either the controls or the subjects taking hypnotic doses.

Table 3 lists the individual antipyrine half-life values obtained before, during and after barbiturate or Mandrax withdrawal. With the barbiturate group, the means for assays I, II and III are significantly ($P<0{\cdot}001$) lower than our control values (Table 2). There is no significant difference between the results for I and II ($P>0{\cdot}05$), but the mean value for III is longer than that for II ($P>0{\cdot}01$). In the two patients in whom assay IV was carried out while they were free from barbiturates, the results are markedly longer and are very close to the mean for controls. With the Mandrax patients, a similar pattern of results was obtained.

Table 4 lists the urinary output of 6β-OHF and total 17-OHCS in 4 of the barbiturate-dependent patients on full drug dose together with values for 14 control, drug-free subjects. The mean 6β-OHF output expressed either in absolute terms or as a ratio to total 17-OHCS was approximately three times that in the control group ($P<0{\cdot}001$).

TABLE 3. *Plasma antipyrine half-life in patients dependent on and withdrawn from barbiturates or Mandrax*

Barbiturate-dependent patients	Plasma antipyrine half-life (h) I (full dose)	II (50% dose)	III (drug free, 7 days)	IV (drug free, 37 days)
A	6·4	2·5	4·7	—
B	3·8	3·3	7·7	12·1
C	6·5	5·4	—	—
D	5·0	5·7	9·0	—
E	4·2	4·1	5·4	—
F	5·0	4·5	6·0	6·2*
G	4·4	6·0	—	—
H	7·1	5·2	7·7	10·4
Mean ± S.D.	5·3±1·2	4·6±1·2	6·8±1·6	11·3
Mandrax-dependent patients				
I	8·4**	—	—	—
J	5·4	5·8	7·2	—
K	4·7	5·5	6·7	—
Mean	5·1	5·7	7·0	—

For details of withdrawal scheme, see **Methods**. The values asterisked were not included in calculation of the means for the following reasons: * Positive barbiturate in urine screen; ** Not withdrawn.

TABLE 4. *Urinary output of 6β-hydroxycortisol and 17-hydroxycorticosteroids in barbiturate-dependent patients*

Patient	(a) 6β-OHF (mg/day)	(b) 17-OHCS (mg/day)	(a/b) Ratio
A	1·20	6·6	0·18
C	1·32	6·2	0·21
G	0·78	12·3	0·07
H	0·60	7·8	0·08
Mean ± S.D.	1·0±0·3 ($P<0{\cdot}001$)	8·2±2·8 NS	0·14±0·07 ($P<0{\cdot}001$)
Controls (14)	0·32±0·16	9·6±3·3	0·04±0·02

Discussion

The results in Table 2 demonstrate clearly that as a group the barbiturate and Mandrax-dependent patients metabolized antipyrine much more rapidly than did a control population. The mean plasma antipyrine half-life of $4{\cdot}6 \pm 1{\cdot}2$ h in the barbiturate group (Table 3, Assay II) is the shortest value reported to date for a drug-exposed group. This reflects a slightly faster rate of antipyrine metabolism than we have found in two other patients groups in which there is massive drug exposure—epileptics on anticonvulsant therapy and barbiturate overdose patients (unpublished observation). Since barbiturates are known to induce drug-metabolizing enzyme activity in man, it is not unexpected that the large doses taken over a long period of time by dependent subjects should produce this very marked induction. With normal hypnotic doses of amylobarbitone or Mandrax over a short period of time (Table 2), induction does occur but less markedly, the half-life values obtained being intermediate between the control and dependent-subject results. Similar changes have been reported following hypnotic doses of phenobarbitone (Vesell & Page, 1969).

With the other index studied, urinary output of 6β-OHF, the results in Table 4 provide further evidence of marked induction in the dependent patients. Since their total 17-OHCS was within the normal range, the high levels of 6β-OHF probably reflect increased microsomal hydroxylation.

In studying the effect of gradual withdrawal of the hypnotics, the mean plasma antipyrine half-life at Assay II (50% drug dose) was found to be shorter than at Assay I (full drug dose) in 6 of the 8 barbiturate-dependent patients. A possible explanation for this surprising finding is that the clinician's estimate of the patient's drug usage on admission may have been too high and that further induction was occurring in the first few days of 'drug withdrawal'. An alternative possibility is that the same effect may have been achieved by the patients themselves supplementing their scheduled dose during the initial period in hospital. A further possible explanation is that, since inducers are also potential substrates for the microsomal drug-metabolizing enzymes, the high barbiturate dose may have partially inhibited metabolism of antipyrine. The significantly longer half-life at Assay III (drug-free for 1 week) in the barbiturate group probably indicates a decrease in the extent of induction. In patients A and H, this trend was more obvious at Assay IV (drug-free for 5 weeks), the values at this time being close to our mean value for controls. Although only these 2 patients were studied at this time interval after drug withdrawal, it would seem likely that, in contrast with the sub-normal microsomal enzyme activity found in rats after barbiturate withdrawal (Stevenson & Turnbull, 1968), the drug-metabolizing capacity of withdrawn patients returns to normal. The positive barbiturate result in patient F at Assay IV, accounts for the continuing induction in this case.

That the patients at the beginning of the study were drug tolerant was clearly demonstrated by the lack of adverse effect or even in many cases, hypnotic effect, when given their estimated drug requirement. Presumably, their increased drug-metabolizing capacity as indicated by the short half-life of antipyrine is responsible at least in part for this tolerance. Similarly, it is likely that the dependent patients would be tolerant to all drugs which are oxidized in the liver and that they would have a higher dose requirement for these. A rational approach to the use

of other drugs in barbiturate and Mandrax-dependent patients must take into account the grossly increased drug-metabolizing capacity of these patients and the marked reduction that is likely to occur on drug withdrawal.

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