EFFECT OF LONG-TERM PHENOTHIAZINE TREATMENT ON DRUG METABOLISM

T. KOLAKOWSKA & M. FRANKLIN

Littlemore Hospital Research Unit, Department of Psychiatry, University of Oxford, Oxford OX4 4XN

B. ALAPIN

Hill End Hospital, St Albans, Herts

- 1 The half-life of plasma antipyrine was measured in twelve chronic schizophrenic patients during long-term phenothiazine treatment and again following 4-5 weeks on placebo.
- 2 The mean antipyrine half-life was low during phenothiazine administration (6.1 ± 4.2 h), rising after withdrawal of drugs to the range reported for untreated subjects by other authors (9.5 ± 4.2 h). The prolongation of antipyrine half-life following the drug-free period occurred in nine of twelve subjects and the difference was significant for the group at $P < 0.05$.
- 3 The finding suggests that prolonged administration of phenothiazines stimulates the rate of drug metabolism.

Introduction

Potential changes in the rate of drug metabolism produced by phenothiazine treatment might be of clinical importance since it is a common therapeutic practice to combine a phenothiazine derivative with drugs such as other neuroleptics, antidepressants and anticonvulsants. There is some evidence that prolonged administration of phenothiazines affects drug metabolism. Several authors reported increased activity of liver microsomal enzymes in animals pretreated with phenothiazines (Breyer, 1972; Valerino, Vesell, Johnson & Aurori, 1973; Wattenberg & Leong, 1965) and it has been found that chlorpromazine increases meprobamate metabolism in rats (Kato & Vasanelli, 1964).

However, studies in humans suggest that phenothiazines impair rather than induce metabolism of other drugs. Moody, Tait & Todrick (1967) found that the administration of phenothiazines to patients chronically treated with tricyclic antidepressants increased the steady-state plasma levels of the latter. A similar effect on diphenylhydantoin levels has been mentioned by Kutt & McDowell (1968). More recently Gram & Overb (1972) reported that neuroleptic treatment inhibits the metabolism of test doses of radioactive tricyclic antidepressants.

The present study is concerned with the effect of long-term phenothiazine treatment on the plasma half-life of antipyrine. The antipyrine test was chosen as an index of the drug metabolism because it has been widely used to assess the drug-metabolizing capacity and the changes which

result from the induction or inhibition of liver microsomal enzymes by chemical agents.

Methods

Patients

The plasma half-life of antipyrine was measured during long-term phenothiazine treatment and again 28-36 days after drug withdrawal in twelve chronic schizophrenic patients. All had been receiving phenothiazines continuously for several years. Table 1 shows the sex, age and drug regime of the investigated subjects. It was considered justifiable to withdraw medication for 4-5 weeks since in none of the patients was it clear that continuous administration of neuroleptics had a beneficial effect and some suffered side-effects. All patients gave their consent to participate in the study. During the period of drug withdrawal all subjects received a placebo (a 33% aqueous solution of sucrose with infusions of Quassia) and three had nitrazepam (5 mg *nocte*) (N.T., A.P. and M.W.).

Plasma antipyrine half-life

The subjects fasted and had no medication for 12 h preceding the test and during the test. Antipyrine (10 mg/kg) in an aqueous solution diluted with orange juice was given between

07.00 h and 07 h 30 minutes. Food was withheld for a further 2 hours. Blood samples were taken into lithium heparin tubes at 3, 6, 9 and 12 h following the administration of antipyrine. Plasma levels of antipyrine were estimated in duplicate by the method of Brodie, Axelrod, Soberman & Levy (1949). Standard curves (5-50 mg/ml) were linear and the variation between duplicates was from 4.2% for the range of 20-25 mg/ml to 12% for the range of 5-8 mg/ml. Antipyrine half-life was calculated by relating the logarithms of declining plasma antipyrine concentrations to time after drug administration. In eight instances antipyrine concentration was higher at 6 h than at 3 h and the calculation was based on three declining values.

The significance of differences between plasma antipyrine half-life during phenothiazine and after

drug withdrawal was tested by the Wilcoxon sign-rank test of differences (Siegel, 1956).

Results

Table 1 lists the plasma antipyrine half-lives found in twelve patients during long-term phenothiazine treatment and following drug withdrawal, with mean $\pm$ s.d. and range for the group on both occasions. The mean values were 6.1 ± 4.1 h and 9.5 ± 4.2 h respectively, antipyrine half-life being longer following phenothiazine withdrawal. Prolongation of the antipyrine half-life during this drug-free period occurred in nine of twelve subjects. This difference was significant for the group at $P < 0.05$ (Wilcoxon sign-rank test).

Table 1 Plasma antipyrine half-life ($T_{1/2}$) during phenothiazine treatment and following drug withdrawal

Patient	Sex	Age (years)	Medication (mg/day if not stated otherwise)	Antipyrine $T_{1/2}$ (h)	
				On medication	Off drugs
M.C.	F	51	Chlorpromazine 450	2.7*	8.0
W.M.	M	49	Chlorpromazine 300	1.6*	6.0
J.F.	F	55	Chlorpromazine 100	2.9*	16.0
J.H.	M	46	Trifluoperazine 20	2.4	5.1
W.D.	F	58	Trifluoperazine 20	4.6	10.8*
N.T.	M	36	Thioridazine 600	5.0	6.2
O.C.	M	65	Thioridazine 150	2.7*	10.6*
A.W.	M	33	Fluphenazine decanoate 50 mg every 2 weeks	13.5*	18.4
L.T.	M	55	Fluphenazine decanoate 50 mg every 2 weeks	8.8	9.2
M.W.	F	59	Chlorpromazine 150 + Benzhexol 4	11.2	11.1
A.F.	F	55	Chlorpromazine 300	7.4	5.8
A.P.	M	68	Thioridazine 400 + Benzhexol 6	10.8	7.2*
				Mean 6.1 ± 4.1	9.5 ± 4.2
				Range 1.6 – 13.5	5.1 – 18.4

* Antipyrine half-life calculated from three plasma estimations

Table 2 Plasma antipyrine half-life ($T_{1/2}$) reported by other authors

Subjects	Antipyrine $T_{1/2}$ (h) (Mean $\pm$ s.d.)	Range	Number of individuals	Author
Control	12.7 ± 3.3	6.5 – 18.2	32	Vesell & Page (1969)
	12.0 ± 3.5	6 – 22	61	O'Malley, Crooks, Duke & Stevenson (1971)
	11.7 ± 2.9	8 – 17	30	O'Malley <i>et al.</i> (1973)
		5.8 – 21.4	8	Davies, Thorgeirsson, Breckenridge & Orme (1973)
	11.9 ± 1.4	6.9 – 21.1	10	Kadar <i>et al.</i> (1973)
Barbiturate dependent	13.1 ± 7.5	5.2 – 35	26	Kolmodin, Azarnoff & Sjoqvist (1969)
	4.6 ± 1.2	2.5 – 6.0	8	Ballinger, Browning, O'Malley & Stevenson (1969)
Exposed to hydrocarbon insecticides	7.7 ± 2.6	2.7 – 11.7	26	Kolmodin <i>et al.</i> (1969)

Those patients whose antipyrine half-life remained unchanged (M.W.) or shortened (A.P. and N.T.) after a period on placebo did not differ from the rest in their phenothiazine regime, but two of the three had received benzhexol while on phenothiazines and nitrazepam while on placebo.

Table 2 shows the plasma antipyrine half-lives reported by other authors. The results obtained in our patients during the placebo period are close to the control values while the half-lives from the period of phenothiazine administration are similar to the values found in barbiturate-dependent patients and in subjects exposed to insecticides.

In the case of extremely short half-life of 1.6 h (subject M.W., Table 1), plasma antipyrine decreased from peak value of 25 µg/ml at 6 h to 6.5 µg/ml at 9 h and 2.5 µg/ml at 12 hours.

Discussion

The finding of a short plasma antipyrine half-life during phenothiazine treatment and its prolongation after drug withdrawal suggests that the prolonged administration of phenothiazines stimulates drug metabolism. This finding is consistent with phenothiazine activation of liver microsomal enzymes reported in experimental animals. Among activated enzymes were benzpyrene hydroxylase (Wattenberg & Leong, 1965), ethylmorphine demethylase (Valerino *et al.*, 1973) and aniline hydroxylase (Breyer, 1972; Oppelt, Zange, Ross & Remmer, 1970; Valerino *et al.*, 1973). Cytochrome P-450 content was also increased in phenothiazine pretreated animals (Breyer, 1972; Valerino *et al.*, 1973).

In this context, stimulation of its own metabolism by chlorpromazine could account for the decrease in its steady-state plasma levels after 2 weeks treatment with a constant daily dose of this drug. (Sakalis, Curry, Mould & Lader, 1972).

However, this evidence for stimulation of microsomal enzymes is in contrast to reports showing impaired drug metabolism after phenothiazine administration. The contradiction between our finding that phenothiazines reduce antipyrine half-life and the reports that they increase steady-state levels of diphenylhydantoin (Kutt & McDowell, 1967) and of tricyclic antidepressants (Moody *et al.*, 1967) could be due to the more complex effect of phenothiazines on the metabolism of a chronically administered drug than on the metabolism of a test dose of antipyrine.

The inconsistency between the finding that phenothiazines reduce plasma antipyrine half-life, and the reports that they impair metabolism of a test dose of radioactive tricyclic antidepressants (Gram & Overb, 1972) might be related to a more general lack of correlation between the half-life of antipyrine and that of other drugs (Kadar, Inaba, Endrenyi, Johnson & Kalow, 1973).

Data on the effects of tricyclic antidepressants on drug metabolism are no less controversial. The recent work of O'Malley, Browning, Stevenson & Turnbull (1973) did not confirm the inhibitory effect of tricyclic antidepressants, reported by Vessell, Passananti & Greene (1970), and, moreover, Breyer (1972) found imipramine to be a potent inducer of drug metabolizing microsomal enzymes.

The contradictory findings about the effects of psychopharmaca on drug metabolism and the clinical importance of the problem indicate the need for further investigations.

We wish to thank Professor M.G. Gelder and Professor D.G. Grahame-Smith for their help and advice in the preparation of this paper; Drs A.D. Harris and F.J.J. Letemendia for allowing us access to their patients; Mrs E.M. Green and Mrs E. Kuht for nursing assistance. The work was supported by a grant from the Medical Research Council.

References

- BREYER, U. (1972). Perazine, chlorpromazine and imipramine as inducers of microsomal drug metabolism. *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **272**, 277-288.
- BRODIE, B.B., AXELROD, J., SOBERMAN, R. & LEVY, B.B. (1949). The estimation of antipyrine in biological materials. *J. biol. Chem.*, **179**, 25-29.
- BALLINGER, B., BROWNING, M., O'MALLEY, K. & STEVENSON, I.H. (1962). Drug-metabolizing capacity in states of drug dependence and withdrawal. *Br. J. Pharmacol.*, **45**, 638-643.
- DAVIES, D.S., THORGEIRSSON, S.S., BRECKENRIDGE, A. & ORME, E. (1973). Inter-individual differences in rates of drug oxidation in man. *Drug Metabolism and Disposition*, **1**, 411-417.
- GRAM, L.F. & OVERB, K.F. (1972). Drug interaction: Inhibiting effect of neuroleptics on metabolism of tricyclic antidepressants in man. *Br. med. J.*, **1**, 463-466.
- KADAR, D., INABA, T., ENDRENYI, L., JOHNSON, G.E. & KALOW, W. (1973). Comparative drug elimination capacity in man - glutethimide, amobarbital, antipyrine and sulfipyrazone. *Clin. Pharmacol. Ther.*, **14**, 553-560.
- KATO, R. & VASANELLI, P. (1964). Induction of increased meprobamate metabolism in rats pretreated

- with some neurotropic drugs. *Biochem. Pharmac.*, **11**, 779-794.
- KOLMODIN, B., AZARNOFF, D.L. & SJOQVIST, F. (1969). Effect of environmental factors on drug metabolism; Decreased plasma half-life of antipyrine in workers exposed to chlorinated hydrocarbon insecticides. *Clin. Pharmac. Ther.*, **10**, 638-642.
- KUTT, H. & McDOWELL, F. (1968). Management of epilepsy with diphenylhydantoin sodium. *J. Am. med. Ass.*, **203**, 969-972.
- MOODY, J.P., TAIT, A.C. & TODRICK, A. (1967). Plasma levels of imipramine and desmethylinipramine during therapy. *Br. J. Psychiat.*, **113**, 183-193.
- O'MALLEY, K., CROOKS, J., DUKE, E. & STEVENSON, I.H. (1971). Effect of age and sex on human drug metabolism. *Br. med. J.*, **3**, 607-609.
- O'MALLEY, K., BROWNING, M., STEVENSON, I. & TURNBULL, M.J. (1973). Stimulation of drug metabolism in man by tricyclic antidepressants. *Eur. J. clin. Pharmac.*, **6**, 102-106.
- OPPELT, W., ZANGE, M., ROSS, W.E. & REMMER, H. (1970). Comparison of microsomal drug hydroxylation in lung and liver of various species. *Res. Comm. Chem. Path. Pharmac.*, **1**, 43-56.
- SAKALIS, G., CURRY, S.M., MOULD, G.P. & LADER, M.H. (1972). Physiologic and clinical effects of chlorpromazine and their relationship to plasma level. *Clin. Pharmac. Ther.*, **13**, 931-946.
- SIEGEL, S. (1956). *Nonparametric Statistics*. New York: McGraw-Hill.
- VALERINO, D.M., VESELL, E., JOHNSON, A.D. & AURORI, K. (1973). Effects of various centrally active drugs on hepatic microsomal enzymes: A Comparative Study. *Drug Metabolism and Disposition* **1**, 669-678.
- VESELL, E.S. & PAGE, S.G. (1969). Genetic control of the phenobarbital induced shortening of plasma antipyrine half-lives in man. *J. clin. Invest.*, **48**, 2202-2209.
- VESELL, E.S., PASSANANTI, G.T. & GREENE, F.E. (1970). Impairment of drug metabolism in man by allopurinol and nortriptyline. *New Eng. J. Med.*, **283**, 1484-1488.
- WATTENBERG, L.W. & LEONG, J.L. (1965). Effects of phenothiazines on protective systems against polycyclic hydrocarbons. *Cancer Res.*, **25**, 365-370.

(Received August 1, 1974)