PAPERS AND ORIGINALS

Drug Interaction: Inhibitory Effect of Neuroleptics on Metabolism of Tricyclic Antidepressants in Man

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Summary

Total urinary excretion of radioactivity after oral or intravenous administration of a test dose of ^{14}C-imipramine was measured in eight patients. They were tested before, during, and after treatment with neuroleptics. Excretion diminished while the patients were being treated with perphenazine, haloperidol, or chlorpromazine, though not during flupenthixol treatment.

Total urinary excretion of radioactivity and plasma levels of metabolites and unchanged drug were measured in five patients after a test dose of ^{14}C-nortriptyline. Each patient was tested before and again during perphenazine treatment. In all patients perphenazine treatment caused: (1) decrease of total urinary excretion, (2) decreased plasma level of metabolites, and (3) increased plasma level of unchanged nortriptyline.

These results indicate that neuroleptics inhibit the metabolism of tricyclic antidepressants in man.

Introduction

Combined treatment with neuroleptics and tricyclic antidepressants has been recommended in several clinical reports (Davis *et al.*, 1970). It has been used for schizophrenic patients with depressive symptoms and for depressive patients with schizo-affective symptoms. For this reason possible pharmacokinetic interaction between neuroleptics and tricyclic antidepressants was investigated.

Pharmacokinetic drug interaction has been reported to occur in many drug combinations, particularly in respect of the metabolism of drugs rather than their absorption, distribution, or excretion (Anders, 1971). There are relatively few reports on interaction concerning neuroleptics or tricyclic antidepressants.

Chlorpromazine has both stimulatory and inhibitory effects on the metabolism of hexobarbitone in experimental animals (Rümke and Bout, 1960-1). Furthermore, chlorpromazine accelerates the metabolism of meprobamate (Kato and Vassanelli, 1962). Tricyclic antidepressants have been shown to inhibit the metabolism of tremorine and oxotremorine in rats in vitro and in vivo (Hammer and Sjöqvist, 1967). It has also been found that desipramine hydrochloride inhibits the metabolism of amphetamine in isolated, perfused rat liver (Dingell and Bass, 1969). Pretreatment with phenobarbitone decreased steady-state plasma levels of desipramine and nortriptyline in man (Sjöqvist *et al.* 1968). These findings were later confirmed in a twin study (Alexanderson *et al.*, 1969). Forrest *et al.* (1970) found increased urinary excretion of chlorpromazine metabolites when patients were given additional treatment with phenobarbitone. Vesell *et al.* (1970) found that nortriptyline prolonged the plasma half-lives of phenazone (antipyrine) and dicoumarol (bishydroxycoumarin) in man. P. G. Dayton has reported a rise in steady-state plasma level of imipramine and desipramine when methylphenidate was administered concurrently with the imipramine treatment (Cosmides, 1970).

Interaction between neuroleptics and antidepressants has, despite its clinical relevance, not been investigated thoroughly. Moody *et al.* (1967) reported on one patient, who had a rise in plasma levels of imipramine and desipramine when chlorpromazine was given in addition to the imipramine treatment. They did not, however, interpret these findings as being a result of inhibited metabolism of imipramine.

We have previously studied the pharmacokinetic properties of imipramine and in particular the metabolism and urinary excretion of metabolites (Christiansen *et al.*, 1967). Urinary excretion of radioactivity after oral administration of ^{14}C-imipramine was relatively rapid. Over 95% of the excretion takes place as polar metabolites: hydroxymetabolites, glucuronides, and several non-extractable unidentified metabolites. These data were the basis for using total urinary excretion of radioactivity after administration of ^{14}C-imipramine as a measure of metabolism of the drug. The pharmacokinetic interaction between neuroleptics and antidepressants was investigated in this way in an initial study, where, however, the plasma level of imipramine or metabolites could not be determined. Later the drug

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interaction between neuroleptics and antidepressants was studied by measuring plasma levels of unchanged drug and metabolites as well as urinary excretion of radioactivity. ^{14}C-nortriptyline was used as a test substance in these studies since the unchanged form of this compound could be determined in plasma.

Methods and Patients

^{14}C-Imipramine, Initial Studies on Urinary Excretion.—Eight women aged 49-60 took part in the investigation. All were diagnosed as suffering from schizophrenia according to the criteria of Bleuler (1911). A test dose of 3 μCi of ^{14}C-imipramine in a total of 10 mg of imipramine was given by mouth or intravenously. Urinary excretion of radioactivity was measured when the patients were on treatment with neuroleptics and 10-30 days after discontinuation of the drug. Most patients were tested both before and after periods of discontinuation as well as during the period of discontinuation. The influence of perphenazine treatment was tested in five patients, chlorpromazine treatment in one patient, haloperidol treatment in two patients, and flupenthixol treatment in two. Urine was collected at intervals of two to eight hours for 48 hours after administration of the test dose. ^{14}C-imipramine was labelled at the 10-11 position in the central ring system.

^{14}C-Nortriptyline, Studies on Plasma Levels and Urinary Excretion.—Five patients (three men aged 22, 23, and 44 and two women aged 32 and 56) were tested before and during treatment with perphenazine 20-48 mg/day. All patients were diagnosed as suffering from schizophrenia according to the criteria of Bleuler (1911). A test dose of 3 μCi of ^{14}C-nortriptyline in a total dose of 50 mg of nortriptyline was given by mouth. Urine was collected at intervals of four to eight hours for the first 24 hours. Blood samples were drawn at intervals of two to four hours during the first 10-15 hours and then 24 hours after administration of the test dose. ^{14}C-nortriptyline was labelled in position α to the N-atom in the side chain.

ANALYSIS

Radioactivity in urine was measured according to the principles previously described (Gram *et al.*, 1971a). For counting radioactive in plasma 1-ml samples were taken. Soluene (Packard) 1 ml and dioxan 1 ml were added and the plasma was incubated at 50-60°C for 12-16 hours for total solution. Then 450 μl of 1 M HCl and finally 15 ml of Instagel (Packard) were added. The plasma specimens were counted for 100 minutes in a liquid scintillation spectrometer.

After the administration of ^{14}C-nortriptyline counts 50-100% above the background level were obtained. Plasma samples drawn immediately before administration of the test dose were used for background counting. The internal standard was used for all radioactive counting on urine and plasma. Measurement of unchanged nortriptyline in plasma was performed according to the ^{3}H-acetic anhydride coupling technique of Hammer and Brodie (1967). The method was slightly modified by the addition of 0·1 M salicylic aldehyde to the hexane phase in the first step of extraction (Fredricson Overø, 1971). Apart from this modification, by which increased specificity for secondary amines is obtained, the assay was performed as described by Hammer and Brodie. Blind samples and standard curves were run in each experiment.

The specificity of the assay was checked occasionally by thin-layer chromatography in a single solvent system. Only one spot corresponding to the labelled coupling product of nortriptyline was present. The absence of further spots makes it unlikely that hydroxymetabolites were assayed. As the estimation of unchanged nortriptyline was considered specific, and standard curves were run in each experiment, the difference between total radioactivity in plasma and concentration of unchanged drug could be used as an estimate of the total concentration of nortriptyline metabolites in plasma.

Results

The results of the studies on urinary excretion of ^{14}C-imipramine are summarized in Fig. 1. More detailed accounts of these results have been published elsewhere (Gram *et al.*, 1971b). In all patients there was a 25-50% decrease in total urinary excretion of radioactivity after oral administration of ^{14}C-imipramine when perphenazine (20-48 mg/day), haloperidol (12-20 mg/day), or chlorpromazine (300 mg/day) was administered. In two patients on flupenthixol treatment (3-6 mg/day) the urinary excretion was not influenced. The two patients on haloperidol were on concomitant treatment with biperiden. Repeated testing during a period of separate discontinuation of biperiden showed that haloperidol, but not biperiden, inhibited the urinary excretion of radioactivity.

The results of the studies with ^{14}C-nortriptyline are shown in Fig. 2. The inhibition of urinary excretion of radioactivity during perphenazine treatment was the same as that seen in the initial studies. During perphenazine treatment the plasma level of metabolities after administration of a single test dose of ^{14}C-nortriptyline was reduced by 25-60%. The plasma level of unchanged nortriptyline at the same time rose to a level 10-30% higher than that found before the start of perphenazine treatment. There was a pronounced inter-individual variation of all three pharmacokinetic measurements. The change in these measurements in relation to perphenazine administration was, however, identical in all five patients.

Discussion

Theoretically, the observed inhibition of urinary excretion of ^{14}C-imipramine could be a result of drug interaction at various levels: absorption, metabolism, or excretion. The changes that might be expected in the three pharmacokinetic measurements in these cases are shown in the Table. The results of the study

Theoretical Consequences of Different Mechanisms of Neuroleptic-induced Decrease of Urinary Excretion of ^{14}C-Nortriptyline

Mechanism of Drug Interaction	Change		
	Plasma Levels of Nortriptyline		Urinary Excretion
	Unchanged Drug	Metabolites	
Inhibited absorption ..	Decrease	Decrease	Decrease
Inhibited metabolism ..	Increase	Decrease	Decrease
Inhibited renal excretion	Increase	Increase	Decrease

with ^{14}C-nortriptyline strongly suggest that neuroleptic drugs inhibit the metabolism of tricyclic antidepressants. The decrease in the plasma level of metabolites did not equal the rise in the plasma level of unchanged nortriptyline. There is, however, no reason to believe that the metabolites would necessarily show the same pattern of distribution within the body as would the unchanged drug. Indeed the more polar metabolites probably have a smaller volume of distribution, and therefore exhibit a relatively higher plasma concentration, than the unchanged drug. So one should not expect in these experiments a rise in plasma level of unchanged drug to be accompanied by an equal decrease in the level of metabolites. This may also explain why the plasma concentration of metabolites is so much higher than the concentration of unchanged drug.

Other than studying the effect of neuroleptics on steady-state plasma levels of tricyclic antidepressants, it seems difficult

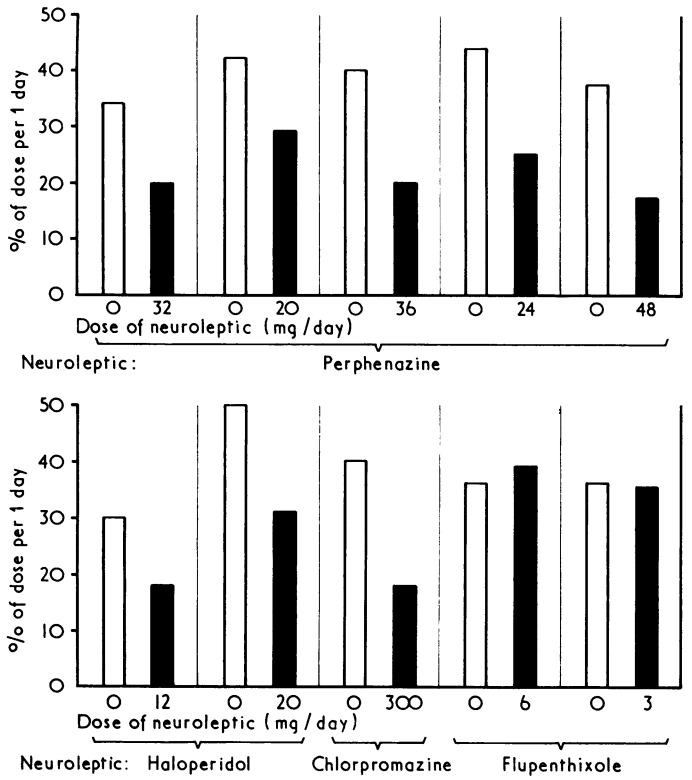

FIG. 1—Urinary excretion of orally administered ^{14}C-imipramine. Total excretion of radioactivity on first day in percentage of dose. Patients in drug-free periods (open columns) and during treatment with neuroleptics (black columns).

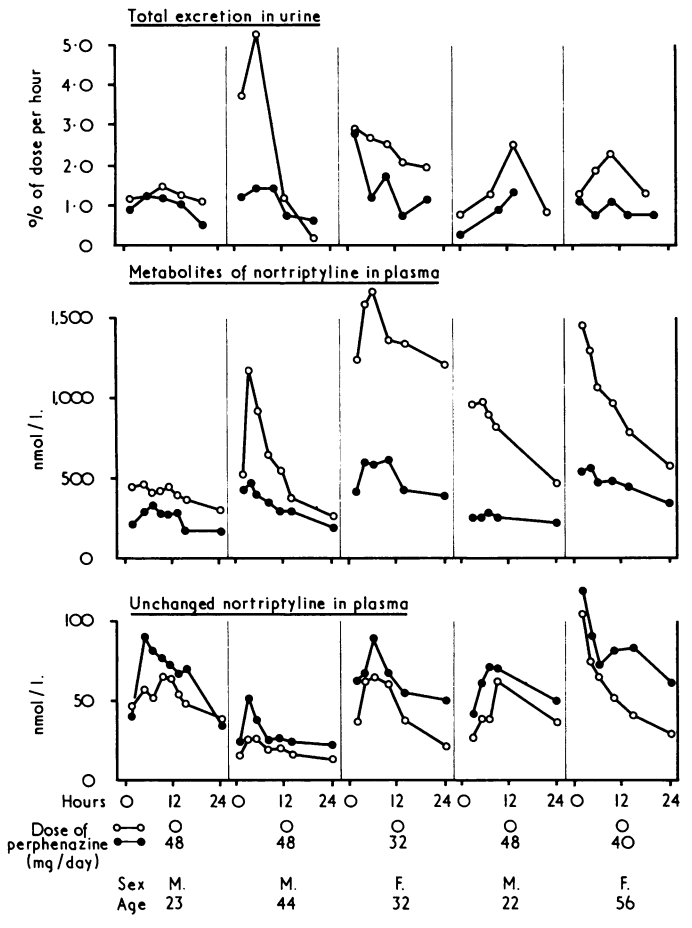

FIG. 2—Urinary excretion in percentage of dose per hour, plasma level of metabolites, and plasma level of unchanged drug in nmol/l. after oral administration of ^{14}C-nortriptyline. Five patients tested in drug-free period (open points) and during perphenazine treatment (black points). Note the difference in scale (by a factor of 10) between concentrations of metabolites and those of unchanged nortriptyline.

to design further studies in man that can throw more light on the drug interaction observed. Analyses of changes in the metabolite patterns in plasma or urine might give valuable information about the mechanism of drug interaction. Experiments on liver homogenate, liver slices, and perfused liver in experimental animals would also be of interest. Studies along these lines are in progress.

It is surprising that clinical signs of interaction between neuroleptics and tricyclic antidepressants have never been reported. However, this may be because the two types of drug exert opposite effects on the central adrenergic synapses, the neuroleptics decreasing the activity by blockade of the receptor and the antidepressants increasing the activity through an inhibition of noradrenaline re-uptake into the neurones.

The influence of the pharmacokinetic interaction on the clinical effect is unknown. Recently a relation between the steady-state plasma level of nortriptyline and the clinical effect has been postulated (Åsberg *et al.*, 1971). Hence possibly neuroleptic drugs can in some way influence the clinical effect of tricyclic antidepressants. Controlled clinical trials with rating scale assessments and with plasma level determinations and different drug combinations are urgently needed.

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References

Alexanderson, B., Price Evans, D. A., and Sjöqvist, F. (1969). *British Medical Journal*, 4, 764.
Anders, M. W. (1971). *Annual Review of Pharmacology*, 11, 37.
Åsberg, M., Cronholm, B., Sjöqvist, F., and Tuck, D. (1971). *British Medical Journal*, 3, 331.
Bleuler, E. (1911). *Dementia Praecox oder der Gruppe der Schizophrenien.* Leipzig and Wien, Deuticke.
Christiansen, J., Gram, L. F., Kofod, B., and Rafaelsen, O. J. (1967). *Psychopharmacologia*, 11, 255.
Cosmides, G. J. (1970). *Science*, 168, 1013.
Davis, J. M., Klerman, G. L., and Schildkraut, J. (1970). In *Psychopharmacology. A Review of Progress 1957-1967*, ed. D. H. Efron. Washington, Public Health Service Publication.
Dingell, J. V., and Bass, A. D. (1969). *Biochemical Pharmacology*, 18, 1535.
Forrest, F. M., Forrest, I. S., and Serra, M. T. (1970). *Biological Psychiatry*, 2, 53.
Fredricson Overø, K. (1971). *Acta Pharmacologica et Toxicologica*, 29, Suppl. No. 4, p. 43.
Gram, L. F., Kofod, B., Christiansen, J., and Rafaelsen, O. J. (1971a). *Clinical Pharmacology and Therapeutics*, 72, 239.
Gram, L. F., Kofod, B., Christiansen, J., and Rafaelsen, O. J. (1971b). In *Proceedings of the VII International Congress of the Collegium Internationale Neuro-Psychopharmacologicum*, ed. O. Vinar, Z. Votova, and P. B. Bradley, p. 194. Amsterdam, Excerpta Medica.
Hammer, W., and Brodie, B. B. (1967). *Journal of Pharmacology and Experimental Therapeutics*, 157, 503.
Hammer, W., and Sjöqvist, F. (1967). In *Proceedings of the First International Symposium on Antidepressant Drugs*, ed. A. Cerletti and F. J. Bové, p. 301. Amsterdam, Excerpta Medica.
Kato, R., and Vassanelli, P. (1962). *Biochemical Pharmacology*, 11, 779.
Moody, A., Tait, C., and Todrick, A. (1967). *British Journal of Psychiatry*, 113, 183.
Rümke, C. L., and Bout, J. (1960-1). *Archiv für experimentelle Pathologie und Pharmakologie*, 240, 218.
Sjöqvist, F., *et al.* (1968). In *Proceedings of European Society for the Study of Drug Toxicity*, ed. S. B. de C. Baker, J. R. Boissier and W. Koll, vol. 9, p. 246. Amsterdam, Excerpta Medica.
Vesell, E. S., Passananti, G. T., and Green, F. E. (1970). *New England Journal of Medicine*, 283, 1484.