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Fluvoxamine-tricyclic antidepressant interaction

An accidental finding

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We report a pharmacological interaction between tricyclic antidepressants (TCA) and fluvoxamine found by accident in three depressed in-patients.

In three patients with major depression (DSM III), only a very partial therapeutic response was obtained after 3 weeks of oral treatment with a single evening dose of a TCA; clomipramine 150 mg/day in one patient, and amitriptyline 125 mg and 150 mg/day in the second and third patients, respectively. The antidepressants were prescribed in association with benzodiazepines (flunitrazepam for one patient, and dipotassium chlorazepate and prazepam for the second and third patients, respectively).

Treatment of resistant depression sometimes requires a combination of two antidepressants, after several modifications of the dosage of the first TCA used. Since 1974, we have routinely monitored the plasma levels of the principal TCA.

Thus, after measurement of the plasma TCA level at steady state (at least 10 days after beginning treatment, in blood sampled 14 h after the evening dose), using a chromatographic method [6], fluvoxamine was prescribed – 300 mg for 2 patients and 100 mg for 1 patient – in combination with the initial TCA and the benzodiazepine. Ten days later the plasma TCA levels were again measured. There was a marked increase in the plasma level of the parent TCA, even though the daily dose was constant or had been slightly decreased (Table 1). The plasma levels were above the therapeutic window [3], without signs of clinical toxicity. The plasma concentration of the metabolite (desmethylclomipramine or nortriptyline) was slightly increased (Patient 1) or decreased (Patient 2 and 3). The result was a marked change in the parent drug/metabolite ratio (6 to 9-fold increase).

This modification in the bioavailability of the TCA is probably due to a drug interaction between the TCA and fluvoxamine. The patients had no medical, liver or kidney disease or other treatment conditions that might have affected biotransformation of the TCA, and technical interference between the fluvoxamine and TCA peaks in the chromatogram was excluded.

Interactions between fluvoxamine and warfarin (65% increase in plasma warfarin) or propranolol (a 5-fold increase in plasma propranolol levels) are known in healthy volunteers (data on file, DUPHAR Laboratories, see Ref. 1). The increased plasma TCA concentration due to

Table 1. Fluvoxamine – tricyclic antidepressant interaction in three patients. CLOMI: clomipramine; AMT: amitriptyline; FLU: fluvoxamine. Steady state plasma levels were measured once during treatment. MR: metabolic ratio

Patients	Treatment	daily dose mg/day		parent drug plasma level ng/ml		metabolite plasma level ng/ml		MR	
		first	second	first	second	first	second	first	second
1 woman 40 y	CLOMI	150	112.5	175	1200	460	550	0.38	2.18
	FLU	0	300						
2 woman 63 y	AMT	125	100	190	380	135	30	1.40	12.66
	FLU	0	300						
3 woman 43 y	AMT	150	150	105	255	155	55	0.67	4.63
	FLU	0	100						

fluvoxamine is a new finding and it is as important as the previously described phenothiazine and valpromide/TCA interactions [5, 7].

The mechanism of the interaction is uncertain. The major site of TCA biotransformation is the liver, where the compounds undergo mainly demethylation and hydroxylation, followed by glucuronide conjugation [4]. Fluvoxamine is metabolized by oxidation, oxidative deamination and hydrolysis into 9 metabolites [2]. As there was an increase in the level of the parent drug, without an increase in the metabolite level increase, it is likely that there was inhibition of the first stage of demethylation.

Whatever the potential importance of the interaction for the efficacy and safety of TCA, fluvoxamine combination treatment needs further assessment and exploration.

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