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Plasma concentrations, information and therapy adherence during long-term treatment with antidepressants

A. C. ALTAMURA & M. MAURI
Department of Clinical Psychiatry, University of Milan, Medical School, Policlinico, Guardia II, via F. Sforza 35, 20122 Milano, Italy

The influence of information on drug plasma monitoring during long-term antidepressant therapy in fourteen ambulant, depressed patients was evaluated as variation in the L/D ratio time course. A larger variability in L/D ratio, with higher coefficient of variation and a poorer clinical outcome, was found in non-informed patients. The data support the hypothesis that verbal information on long-term drug monitoring of antidepressants could improve patients' adherence to therapy.

Keywords plasma concentrations antidepressants therapy adherence

Introduction

Theoretically, drug plasma determination is a suitable tool for studying therapy adherence in patients on long-term treatment with psychotropic drugs.

On the other hand, the provision of verbal or written information about a prescribed drug seems to be an effective strategy for improving therapy adherence with medication (Morris & Halperin, 1979; Ley, 1982). This influence seems to be mediated via its educational content or via an attention-placebo effect (Haynes, 1976). As far as we know, there are no data on the influence of information about the significance and goals of drug plasma determination on therapy adherence during antidepressant drug monitoring studies. The aim of this study was to evaluate whether this kind of information may have a beneficial effect on therapy adherence similar to direct information about medication with antidepressants (Myers & Calvert, 1984).

Methods

The study was performed on 14 ambulant, depressed patients of both sexes (eight men and six women), with ages ranging from 43 to 72 years (mean 55.6 ± 2.15) and suffering from major depression (according to DSM III), diagnosed by two independent psychiatrists. All patients were divided into two groups on the basis of given verbal information (Group 1), or lack of information (Group 2), on the goals of drug plasma monitoring.

The information given to the patients concerned the value of this strategy in improving drug response and reducing side-effects. The allocation of the patients in the two groups was made using the minimization procedure (Taves, 1974), in order to assure comparability of the data in relation to age, sex and treatment. Amitriptyline (AMI), nortriptyline (NTP), imipramine (IMI) and mianserin (MIA) were respectively administered to six, four, two and two patients (Table 1). The clinical picture was evaluated after the first, second, fourth and sixth month of out-patient care using the Hamilton Rating Scale for Depression (HRS-D). The assessment of HRS-D was made by one of us (M. M.) blind to which group the patient belonged.

On the same occasion, heparinized blood samples were collected in the morning 12 h after

Correspondence and reprint requests: Dr A. C. Altamura, Associate Professor of Psychiatry, Department of Clinical Psychiatry, University of Milan, Medical School, Policlinico, Guardia II, via F. Sforza 35, 20122 Milano, Italy

Table 1 Plasma concentrations (PC) during the follow-up period and patient details

					Time (months)							
					1		2		4		6	
	Patient	Drug	Sex	Age (years)	Dose (mg kg^{-1})	PC (ng ml^{-1})	Dose (mg kg^{-1})	PC (ng ml^{-1})	Dose (mg kg^{-1})	PC (ng ml^{-1})	Dose (mg kg^{-1})	PC (ng ml^{-1})
Group 1	1	MIA	F	48	0.68	34	1.01	49	1.16	62.6	1.14	49
	2	AMI	F	53	0.94	46	1.25	57	1.25	56	1.25	55.8
	3	AMI	M	54	1.23	100	1.14	91	1.47	107.9	0.81	52
	4	AMI	M	49	1.19	74.4	1.19	61	0.79	34	1.58	63.7
	5	NTP	M	54	1.00	88	1.00	81	1.00	75	0.40	30
	6	NTP	F	60	1.28	94.7	0.96	59	1.28	79	1.28	93
	7	IMI	M	57	3.80	300	3.00	220	3.00	150	1.60	75
	Mean s.e. mean			53.5 ± 1.58								
Group 2	1	MIA	F	70	0.69	46	0.69	70	0.69	85	0.55	27
	2	AMI	F	72	0.89	73.7	0.89	41	0.89	80	0.62	86
	3	AMI	M	55	1.29	115	1.29	20.5	0.58	72.5	0.23	45
	4	AMI	M	59	1.50	75	1.00	60.0	1.4	124	1.4	125
	5	NTP	M	45	0.80	157	0.8	57.4	0.64	27	0.32	41
	6	NTP	F	43	0.90	27.45	0.9	54.5	0.63	56	0.36	20
	7	IMI	M	60	1.40	180	1.4	147.0	1.4	177.5	1.4	225
	Mean s.e. mean			57.7 ± 4.2								

the last drug intake; these were centrifuged at 2000 rev min^{-1}, and the plasma was stored at −20°C until it was analysed by a gas chromatographic method using a nitrogenphosphorus detector (Rovei *et al.*, 1980; Altamura *et al.*, 1982). Therapy adherence was measured as level-dose ratio (L/D) time course variability. The data were evaluated by performing analysis of variance to a randomized block design and Dunnett's test.

Results

Plasma levels during the follow-up period are shown in Table 1. The two groups differed markedly in the intraindividual and interindividual L/D ratio time course variability (Figure 1). In fact, the coefficient of variation of L/D ratio as the s.e. mean, were higher in non-informed patients than in informed ones (Table 2). In particular the coefficient of variation represents a highly reliable index for evaluating the variability existing among parameters of similar or different kinds.

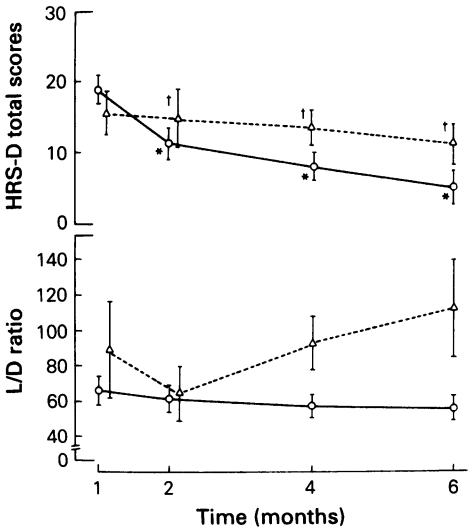

Figure 1 The HRS-D total score and L/D ratio in informed (○) and non-informed (△) patients
* $P < 0.01$, † NS.

The HRS-D total scores showed a significant ($P < 0.01$) improvement in Group 1, and were unchanged in Group 2 (Figure 1).

Discussion

The L/D ratio variability—probably reflecting the therapy adherence—seemed to be lower in

informed patients than in non-informed patients.

On the other hand, clinical outcome seemed to be significantly influenced by adherence to therapy, but since both groups fell below score 15 in the HRS-D by the second month, no definite conclusions can be drawn. This latter finding is in accordance with the data by Loo *et al.* (1980), reporting the outcome to be inversely related to plasma concentration fluctuations during long-term therapy with antidepressants. In Group 1, the reduction in L/D ratio could be explained both in terms of 'physiological' loss in therapy adherence, and/or liver enzyme autoinduction due to the drug itself, or to occasionally associated drugs (i.e. neuroleptics, barbiturates etc.).

In Group 2 the trend to an increase in L/D ratio after an initial fall seems to be explained as drug self-administration because of poor clinical improvement. Moreover, in some patients of Group 2 the onset of more pronounced side-effects led the physicians (blind of the plasma concentration values) to progressively reduce the prescribed dose during the trial.

In conclusion, this study demonstrates that counselling and educating a patient, as well as his closer involvement in the therapeutic management, improves adherence to therapy during long-term antidepressant treatment.

Table 2 The coefficient of variation of L/D ratio expressed as s.e. mean

	Time (months)			
	1	*2*	*4*	*6*
Informed	22.3	23.9	22.6	27
Non-informed	60.2	47.1	30.9	46.6

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