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Relationship between Clinical Effects, Serum Drug Concentration, and Concurrent Drug Interactions in Depressed Patients Treated with Citalopram, Fluoxetine, Clomipramine, Paroxetine or Venlafaxine

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The relationship between clinical effects and plasma concentrations of citalopram, fluoxetine, clomipramine, paroxetine and venlafaxine was studied in 119 cases of major depression. Clinical effects were evaluated using the Clinical Global Impression (CGI) improvement scale. Antidepressants were quantified by a separative chromatographic methodology. Plasma concentrations in responder patients were compared with the plasma concentrations proposed in literature as effective values. We found that the usual therapeutic window is convenient for citalopram and clomipramine, but could be reduced for fluoxetine and increased for venlafaxine and paroxetine. Concurrent drug interactions were also evaluated and clomipramine or citalopram plasma levels were found to be influenced by the presence of associated drugs. A larger study is needed, taking into account not only plasma concentrations and clinical effects, but also some pharmacokinetic data, especially the metabolic activity characterising the patient, and the presence or not of associated drugs.

KEY WORDS — depression; plasma concentration; clinical effect; dose–response relationship; drug interactions

INTRODUCTION

Since the discovery of imipramine by Kuhn in 1958, our ability to treat depression has improved with the availability of receptor-specific and chemically diverse antidepressant substances. Clinical trials with antidepressant medications have shown that, overall, these drugs are effective in about two-thirds of patients (Fawcett and Barkin, 1997). However, most short-term studies indicate that more than 20 per cent of depressed patients remain resistant to treatment (Ananth, 1998). Therefore several therapeutic strategies have been developed, such as increased doses, alternative classes or combination of drugs (Thase and Ruish, 1997). It is important to clearly differentiate between a true resistance to the treatment and a premature discontinuation of drug intake due to side effects or because the patient is frustrated in not responding quicker to the therapy. Compliance with treatment is thus an essential factor in the successful recovery of depression (Montgomery and Kasper, 1998). This is the first reason to make individual therapeutic drug monitoring. In addition, drug doses administered to patients are often inadequate, highlighting the importance of measuring serum levels of antidepressants. Indeed, among general practitioners who usually provide the first line of treatment, at least 35 per cent of initial antidepressant trials are not prescribed for an adequate duration or at an adequate dosage level (Shasha *et al*., 1997). It is also of clear importance to avoid the use of non justified high doses. The implication is that, for every antidepressant, a minimal effective dose can be defined (Benkert *et al*., 1996).

The relationship between clinical effects and plasma concentrations of antidepressant drugs remains a perplexing problem. Variations in phar-

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macokinetics and other important factors are likely to confound the results of studies and impair the determination of efficacy (Benkert *et al*., 1996). Antidepressant drugs are extensively metabolised and their biotransformation pattern has an important influence on their clinical properties (Meyer *et al*., 1996). Reliable data should be available to establish the clinical relevance of plasma concentration measurement and to anticipate and avoid pharmacokinetic drug interactions when prescribing drugs in association.

In order to effectively evaluate the relationship between the clinical effects and the drug's plasma concentration, a study in depressed patients treated with citalopram, fluoxetine, clomipramine, paroxetine or venlafaxine has been conducted. This work is the first part of a large study initiated on the clinical efficacy of several antidepressant drugs. The results of the retrospective evaluation are presented here and an extended prospective study is now on the way.

METHODS

Subjects

The present study was conducted in 119 depressed patients hospitalised in the Psychiatric Unit of the University Hospital in Liège (Belgium). The patients were between 22 and 79 years of age (mean: 47·6, SD: 12·7). Inclusion criteria were a major depressive episode according to DSM-IV (American Psychiatric Association, 1995) and a Montgomery and Asberg Depression Rating Scale (Montgomery and Asberg, 1979) score of 21 or more. The mean duration of hospitalisation was 5 weeks. Antidepressant drugs tested were citalopram, fluoxetine, clomipramine, paroxetine or venlafaxine, depending on the clinical profile of the patients.

A total of 119 patients were enrolled and allocated to treatment (the choice of the antidepressant was based on previous successful treatment with the same antidepressant, negative feedback with another molecule, specific matching between patient's troubles and the antidepressant, etc.): 13 to citalopram, 28 to fluoxetine, 30 to clomipramine, nine to venlafaxine and 39 to paroxetine (Figure 1).

Assessments

Efficacy of treatment was assessed through a comparison between the baseline (start of active treatment) and the end of the hospitalisation using the Clinical Global Impression (CGI) improvement scale. All raters were blind to drug plasma levels. Patients were classified as responders if the CGI score at the end of the evaluation was 1 or 2 (very much or much improved).

At steady state (e.g. after minimum seven times the half-life of the drug), blood samples were collected and plasma concentrations of antidepressant drugs were measured in duplicate by the GC–MS method previously described (Charlier *et al*., 1999). Finally, all the associated medications were recorded, except for drugs administered only one or two times during the stay in hospital.

Statistical analyses

Statistical analyses were conducted with the SAS 6·12 system. Antidepressant plasma levels were normalised by logarithmic transformation. The relation between the drug plasma concentration and the administered regimen was tested using the correlation coefficient and a linear regression. The impact of the presence of other drugs on the plasma level was evaluated by means of the multiple regression method.

The description of the drug plasma concentrations obtained in treatment responders was made by calculation of median and centiles 2·5 and 97·5 in order to include 95 per cent of the results.

RESULTS

Table 1 shows the distribution of responders and non-responders, based on the CGI scores, for each drug at the end of the evaluation.

A significant correlation between drug plasma concentration and oral doses was found for all the antidepressant drugs (Figure 2), with, in the case of citalopram and clomipramine, a moderate influence of other classes of associated drugs. The multiple regression method indicated the linear relations summarised in Table 2. For citalopram, the group of drugs moderately influencing plasma level was neuroleptics. For clomipramine, the influence of two classes of drugs was statistically significant: other antidepressants ($p = 0{\cdot}05$) and antihistamines ($p = 0{\cdot}02$).

The analysis of data collected for clomipramine showed three associations with maprotiline (one responder, two non-responders). An association between clomipramine and venlafaxine was noted

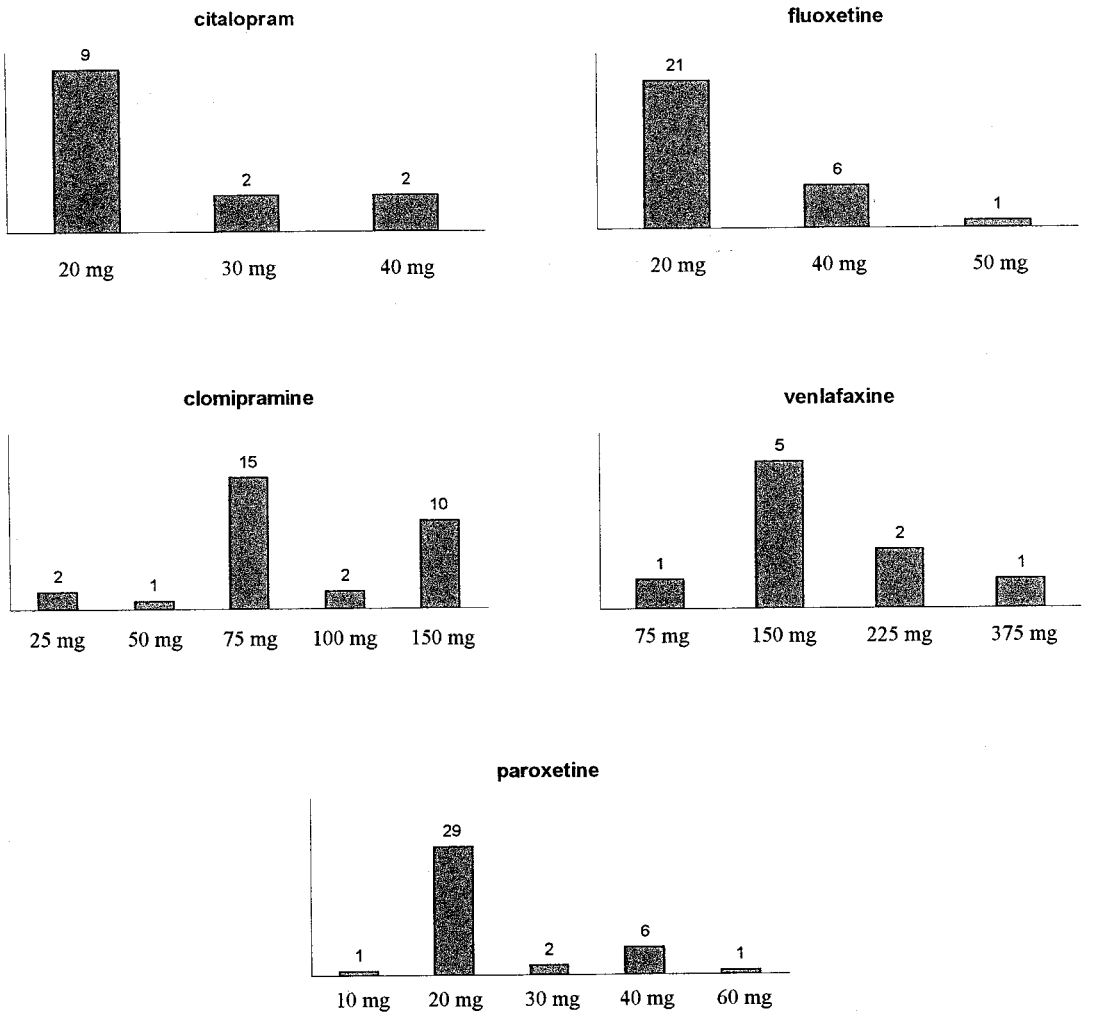

Figure 1. Distribution of antidepressant daily doses (mg) in the study population

Table 1. CGI improvement at the end of the evaluation

	Responders		Non-responders	
	N	Daily doses mg mean (min–max)	*N*	Daily doses mg mean (min–max)
Citalopram ($N = 13$)	6 (46·15%)	25·0 (20–40)	7 (56·85%)	24·0 (20–40)
Fluoxetine ($N = 28$)	8 (28·57%)	27·5 (20–40)	20 (71·43%)	24·5 (20–50)
Clomipramine ($N = 30$)	10 (33·33%)	107·5 (75–150)	20 (66·6%)	92·5 (25–150)
Venlafaxine ($N = 9$)	7 (77·8%)	150·0 (75–225)	2 (22·20%)	300·0 (225–375)
Paroxetine ($N = 39$)	22 (56·41%)	25·9 (10–60)	17 (39·00%)	22·3 (20–40)

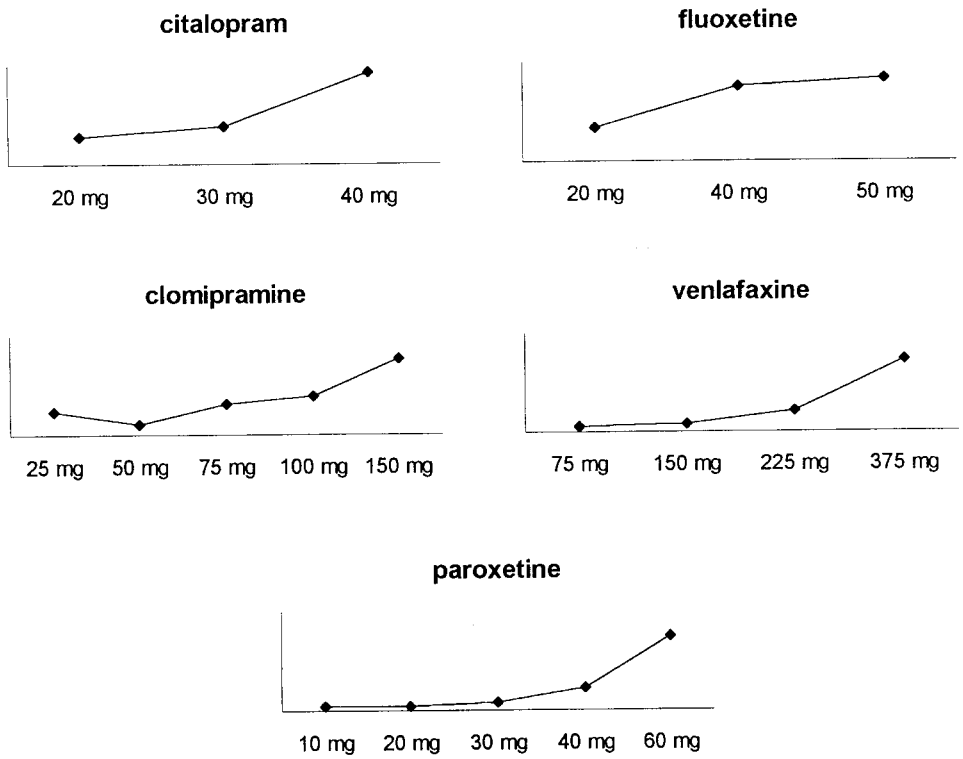

Figure 2. Relationship between drug plasma concentration and oral daily doses (mg)

Table 2. Multiple regression analyses of plasma concentration and posology, in the presence of associated drugs

	a	b	c	d
Citalopram	1·740	0·0587 ($p < 0·0001$)	0·4095 ($p = 0·1021$)	–
Fluoxetine	3·500	0·045 ($p = 0·0010$)	–	–
Clomipramine	3·412	0·0072 ($p = 0·0044$)	0·4842 ($p = 0·0475$)	0·7244 ($p = 0·0169$)
Venlafaxine	2·033	0·011 ($p = 0·0083$)	–	–
Paroxetine	1·3407	0·0768 ($p < 0·0001$)	–	–

ln (plasma conc.) = a + b × dose + c (presence of other drug group I) + d (presence of other drugs groups II)
For citalopram, group I = neuroleptics.
For clomipramine, group I = other antidepressants; group II = antihistamines.

for one patient, another one between clomipramine and fluoxetine, and another one between clomipramine and fluvoxamine. Finally, one patient received simultaneously clomipramine and viloxazine.

Antihistamines used were loratidine, dimetindene, omeprazole, terfenadine and cetirizine.

Drug plasma concentrations at the steady state in the group of responders are presented in Table 3 by means of a non-gaussian approach. Centiles 2·5

Table 3. Plasma concentrations (μg/l) at steady-state in the responder group

	Median concentration	Centile 2·5%	Centile 97·5%
Citalopram	22·65	13·75	62·88
Fluoxetine	59·10	27·56	292·73
Clomipramine	58·85	13·13	319·66
Venlafaxine	44·23	24·71	400·29
Paroxetine	20·15	3·84	185·00

and 97·5 were used to determine theoretical therapeutic intervals which can be compared to those proposed in the literature. However, a new concept that seems to be better adapted to antidepressant drugs is the TCI, target concentration intervention (Holford, 1999). It is argued that the idea of a therapeutic range has limited the interpretation of measured drug concentrations because of an oversimplified pharmacokinetic model, so TCI is proposed as an alternative conceptual strategy. Table 4 summarises the comparison between these different data.

DISCUSSION

The results of this study first confirm that for all the studied antidepressants, there is a statistically significant correlation between oral doses and plasma drug concentrations. This work was thus conducted to evaluate the clinical potential of five antidepressant drugs considering their effective serum levels. In 119 depressed patients included in the study, the response rate at the end of the hospitalisation appears to differ markedly for venlafaxine (77·8 per cent responders) and paroxetine (56·4 per cent responders), from citalopram (46·2 per cent responders), fluoxetine (28·6 per cent responders) and clomipramine (33·3 per cent responders).

For each drug, plasma concentration in responder patients was compared with the plasma concentrations announced in previous studies as effective values. For citalopram, the centiles 2·5 and 97·5 are included in the therapeutic range proposed by Uges (1996) and can be used as a reference. Moreover, these values are much lower than the maximum target concentration (300 μg/l). Concerning fluoxetine, the concentrations in treatment responders vary from 28 to 300 μg/l, which is lower than the 500 μg/l proposed elsewhere (Uges, 1996; Baumann, 1990). These concentrations allow the use of lower daily intakes in order to avoid side effects. Further investigations are needed since Goodnick has reported a non-linear relation between clinical improvement and serum level for fluoxetine (Goodnick, 1994), while other authors denied this relation (Beasley *et al*., 1990; Kelly *et al*., 1989). Concerning clomipramine, our results (13–320 μg/l) are in agreement with the combination of both therapeutic ranges proposed by Uges (1996) and Baumann (1990) since the lower and upper values are respectively 50 μg/l and 300 μg/l. Anyway, these values are lower than the maximum target concentration fixed at 400 μg/l (Flanagan, 1998). We propose to adjust the therapeutic range to 50–300 μg/l. This proposal is enforced by the relation between drug level and clinical response generally admitted for clomipramine (de Oliveira *et al*., 1989). The situation is quite different for venlafaxine and paroxetine. The maximum TCI for venlafaxine was proposed at 100 μg/l, while our responder patients are dispersed between 25 and 400 μg/l. No significant side effects were noticed for patients with the highest values, suggesting that perhaps the therapeutic range could be increased. Further investigations, including more patients and for a longer period of time,

Table 4. Comparison of centiles (2·5%–97·5%) in the responder group (μg/l) with therapeutic range (μg/l) and maximum TCI (μg/l) proposed in the literature (a = Uges, 1996; b = Baumann, 1990; c = Flanagan, 1998)

	Centiles (2·5%–97·5%)	Therapeutic range	Maximum TCI
Citalopram	13·75–62·88	25·00–110·00 (a)	300·00 (c)
Fluoxetine	27·56–292·73	150·00–500·00 (b)	500·00 (c)
Clomipramine	13·13–319·66	50·00–150·00 (a) 150·00–300·00 (b)	400·00 (c)
Venlafaxine	24·71–400·29	–	100·00 (c)
Paroxetine	3·84–185·00	10·00–75·00 (a)	100·00 (c)

should be conducted in order to confirm this observation. Finally for paroxetine, the results obtained in responding patients are higher than the therapeutic range, and the same conclusion as for venlafaxine could be made.

Concerning concurrent drug interactions, pharmacokinetic data have to be considered. Antidepressants are metabolised by cytochrome P450 enzymes, so genetic polymorphism of these CYP450 enzymes may affect the bioavailability. Moreover, inhibition of CYP450 may occur under the influence of many drugs. Fluoxetine and paroxetine are potent *in vitro* inhibitors of cytochrome P450 2D6 which is implicated in the biotransformation of clomipramine. Venlafaxine seems to be associated with a lower risk of clinically significant drug interactions than serotonin specific recapture inhibitors (SSRIs) (Owen and Nemeroff, 1998). In the present study, we report the influence of other antidepressants and antihistamines on the plasma level of clomipramine and of neuroleptics on citalopram plasma concentration. Other studies are needed to assess more accurately the risk of such untoward drug–drug interactions with the antidepressants, particularly in genetically different metabolisers.

Nevertheless, most antidepressants in clinical practice are safe and relatively well tolerated. If efficacy is often satisfying, some patients experience a return of depressive symptoms, despite the constant maintenance dose of antidepressant. Other patients are non-responders, and the time necessary to decide to change the treatment could be reduced if the physician had the assurance that the failure has to be attributed to the drug, not to a poor compliance of the patient or an underestimation of the posology needed. In this way, pharmacokinetic data should be considered at the beginning of the treatment, and patients who are rapid metabolisers might receive higher doses of a drug for optimal therapy. Our study has demonstrated that the classical therapeutic values could be discussed, especially for drugs like venlafaxine or paroxetine. A larger study is now being conducted, with clinical evaluation of the patients with diverse scales, with phenotyping and sometimes genotyping of patients at the beginning of the treatment and with follow-up even after patients have left the hospital. Patients should be divided into several groups according to their characteristics as responders, partial responders with or without relapse, or non-responders, the presence or absence of interacting drugs, and also the metabolic activity of the cytochromes. We hope these observations will help to clarify the relationship between all the parameters able to modify the plasma level of a drug and consequently its efficacy.

In conclusion, many clinical trials of antidepressant medications have shown that unpleasant symptoms can induce the non-compliance of the patients (Demyttenaere, 1997). In fact, compliance with treatment is an essential factor in the successful treatment of depression (Montgomery and Kasper, 1998). When prescribing these medications, the clinicians must be aware that side effects will cause dropout of some patients, interfering markedly with recovery. Consequently, it is important to use therapeutic ranges as narrow as possible, in order to avoid side-effect induction.

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