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Therapeutic drug monitoring of trazodone: are there pharmacokinetic interactions involving citalopram and fluoxetine?

M. Prapotnik[1], R. Waschgler[2], P. König[1], W. Moll[2] and A. Conca[1]

[1]*Department of Psychiatry I, Regional Hospital of Rankweil, and*
[2]*Medical Central Laboratory, Feldkirch, Austria*

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Abstract. Objective: Therapeutic drug monitoring (TDM) of the new generation antidepressants is subject of controversial discussion. Nonetheless, TDM may safeguard against drug-drug interactions, can be used to control compliance and is valuable in the investigation of overdose. Method: The aim of this prospective study was to investigate serum levels of trazodone when prescribed as monotherapy or when used in combination with the selective serotonin reuptake inhibitors citalopram and fluoxetine in a simultaneous assay using high-performance liquid chromatography (HPLC). Over a 1-year period, we studied 97 patients (63 females) with depressive syndrome who were subdivided into 3 main diagnostic groups. Fifty-two patients were smokers, the mean age was 39.9 years and the mean weight was 72.4 kg; 40 patients were taking trazodone alone, 41 trazodone in combination with citalopram and 16 patients trazodone in combination with fluoxetine. Results: The use of citalopram and fluoxetine in combination with trazodone had no significant impact on trazodone serum levels, and the same was true for differences in body weight and smoking behavior. On the other hand, age and sex had a significant influence on the pharmacokinetic pattern of trazodone, causing higher concentrations in females and in older patients. Since the polypharmacy investigated did not change the serum levels of trazodone, we assume that there is no metabolic interaction between trazodone and citalopram and trazodone and fluoxetine. We observed none of the adverse effects which might have been expected, including dizziness, severe headache, daytime sedation, fatigue or the serotonin syndrome even in a mild form. Conclusion: A "double-tracked" antidepressive treatment using trazodone and the SSRIs citalopram and fluoxetine is associated with a wide safety margin.

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Correspondence to
Dr. M. Prapotnik
Department of
Psychiatry I, Rankweil
Regional Hospital,
Valdunastraße 16,
A-6830 Rankweil,
Austria
michael.prapotnik@vol.at

Introduction

The importance of therapeutic drug monitoring (TDM) of the new antidepressive drugs such as the selective serotonin reuptake inhibitors (SSRIs) is the subject of controversial discussion [Baumann 1996, Benfield 1986, Greenblatt et al. 1987, Kelly et al. 1989, Milne and Goa 1991, Preskorn 1993, Sommi et al. 1987]. Most published studies find no evidence for a "therapeutic window". Another unresolved pharmacodynamic question is the correlation between drug serum levels and side effects [Hilton et al. 1997, Sternbach 1991]. However, under present-day clinical conditions, TDM offers information about drug interactions, insufficient therapeutic effect, side effects, compliance and overdose.

In clinical routine, trazodone is frequently prescribed as an additional hypnotic or to augment therapy in patients taking SSRI [König et al. 1999, Nierenberg et al. 1992], but the literature on the pharmacokinetic aspects of trazodone is sparse. The study reported here is an investigation of the concentration/dose ratio of trazodone under monotherapy conditions and in combined therapy with citalopram and fluoxetine in patients affected by depressive syndromes (defined according to the International Classification of Diseases-10, Chapter V (F) (ICD-10). The pharmacological profiles of these compounds and the clinical features including indications, dosage, side effects and safety, are well described in the medical literature [Benfield 1986, Bjerkenstedt et al. 1985, Brösen and Naranjo 2001, Feighner and Boyer 1988, Montgomery et al. 1992, 1993, Nierenberg et al. 1994, Ott and Ott 1985, Small and Giamonna 2000, Sommi et al. 1987, Warsh

Table 1. Concentration (C)/dose (D) ratio and D/weight (W) ratio for trazodone monotherapy and trazodone in combination with citalopram and fluoxetine.

	Mean C/D ratio*	MeanD/W **
Trazodone (T) (n = 40)	5.43 ± 3.2	2.45 ± 1.1
T + citalopram (n = 41)	6.96 ± 5.6	2.40 ± 1.2
T + fluoxetine (n = 16)	6.94 ± 2.9	2.58 ± 1.1

* = Kruskal-Wallis: n = 97 df 2, H = 2.372, p < 0.3,
** = Kruskal-Wallis: n = 97 df 2, H = 0.914, p < 0.9.

and Engelhardt 1992]. The TDM of these drugs was performed simultaneously using high-performance liquid chromatography (HPLC) in cooperation with the Central Medical Laboratory of Feldkirch [Waschgler et al. 2002].

Patients and methods

Ninety-seven patients (63 females) with depressive syndrome and belonging to 3 different main diagnostic groups (63% depressive disorders (n = 61), 24% posttraumatic stress disorders (n = 23) and 13% somatoform disorders (n = 13)) were treated either with trazodone alone or trazodone combined with citalopram or fluoxetine; in the add-on therapy, trazodone was additionally prescribed as a hypnotic (n = 25) or was used in an augmentation strategy (n = 32). The latter condition was defined using the classification of Thase and Rush [1995]: these patients had to be classified at stage 4 of treatment resistance, indicating a failure to respond in 2 different and relevant monotherapy trials with antidepressants having different pharmacological profiles and the failure to respond in a second augmentation strategy. The choice of individual daily dosages depended on the indications mentioned and the clinical requirements and ranged from 50 – 500 mg for trazodone, from 10 – 60 mg for citalopram and from 20 – 80 mg for fluoxetine. Drug blood level measurements were determined under steady state conditions, achieved by prescribing stable dosages over a period equal to 4 – 5 time the half-life of each substance [Riederer and Laux 1992]. The steady state concentrations were defined according to the results of our previous investigations [Conca et al. 1996, Waschgler et al. 2002] and other published studies [Baumann 1992, Eap and Baumann 1996]. These values were for trazodone 300 – 2,500 ng/ml, for citalopram 35 – 150 ng/ml and for fluoxetine 150 – 500 ng/ml. The blood samples were drawn before the morning medication, at least 12 hours after the last administration and therefore represented trough concentrations [Riederer and Laux 1992]. The reversed-phase HPLC technique has been described by Waschgler et al. [2002].

The study was designed as a prospective clinical trial lasting 1 year. Age, sex, body weight, psychiatric diagnostic classification, mode of application (orally or intravenous), applied dosage, duration of therapy, serum levels, concentration/dose ratio (C/D) and comedication were documented. The patients were also subdivided into smokers and nonsmokers. An objective assessment of adverse effects was carried using the "UAW scale" [Grohmann et al. 1994].

Results are presented as mean values ± standard deviation (SD). The nonparametric Kruskal-Wallis H-test was used in the analysis of concentration/dose ratio data. Multiple regression analysis was used for evaluation of the effects of age, sex, body weight and smoking behavior on the concentration/dose ratio of trazodone. The ANCOVA analysis of covariation was performed for each of these variables (Bonferroni correction). The nonparametric Mann-Whitney U-test was applied in comparison with the selected variables within the groups [Sachs 1992].

Results

The mean age of the 97 patients in the study was 39.9 years (SD ± 11.8) and the mean weight was 72.4 kg (SD ± 20.7); 52 of the patients were smokers. A total of 40 patients were taking trazodone alone, 41 were taking trazodone in combination with citalopram and 16 patients with fluoxetine. Monotherapy with trazodone and the combination therapy with one of the SSRIs did not change the concentration/dose ratio and the dose/weight ratio of trazodone (Table 1). Table 2

Table 2. C/D ratio of trazodone according to age, sex, weight and smoking behavior.

N = 97	96	0.386	0.18
Analyses of variance	df	F	p
Age × sex × weight × smoking behavior	4	4.028	0.0047
Age × sex	2	7.968	0.0006
Weight × smoking behavior	2	0.775	0.464

shows the relevant pharmacokinetic variables according to age and sex, calculated using multiple regression analysis and analysis of covariance. Neither the combined drug treatments ($n = 97$, df 2, $H = 2.372$, $p < 0.3$) nor the body weight or the smoking behavior (df 2, $F = 0.775$, $p < 0.5$) showed a significant impact on trazodone serum levels. Age and sex, on the other hand, had a significant influence on the pharmacokinetic profile of trazodone (df 2, $F = 7.968$, $p < 0.0006$) where there were higher trazodone concentrations in females and in older patients. The dose/weight ratio, however, was not affected by sex, age and smoking behavior.

Discussion

Trazodone is a substrate for CYP 450 3A4 [Rotzinger et al. 1998]. SSRIs such as paroxetine, fluoxetine and fluvoxamine display greater in vitro inhibition of CYP 3A4, CYP 2D6, CYP 2C19 and CYP 1A2 than citalopram and this is reflected in their drug interaction profiles [Markowitz 1997, Sproule et al. 1997]. Although no statistically significant differences between mono- and combination therapy were found, the mean concentration/dose ratios were nearly 30% higher in the add-on modality than in the trazodone monotherapy. When more than one CYP enzyme mediate either the same or different metabolic pathways, this does not necessarily mean that each of the enzymes contributes equally to the elimination of the drug [Preskorn 1996]. Maes et al. [1997] attributed a significantly increased plasma concentration of trazodone and m-chlorophenylpiperazine (mCPP) – its principal metabolite – in 27 patients to the addition of fluoxetine to the therapeutic regimen. They concluded that the higher plasma levels of trazodone and mCPP may contribute to the clinical efficacy of the combination with this SSRI. It is noteworthy that in our sample neither body weight nor smoking influenced the C/D ratio of trazodone [Desai et al. 2001, Zevin and Benowitz 1999]. Nonetheless, body weight appears to be an important indicator for dosage selection since the volume of drug distribution is larger (trazodone, like other psychoactive drugs, is lipophilic in character) and the half-life is longer in obese patients [Greenblatt et al. 1987]. In our sample, gender and age were apparently associated with the activities of metabolic pathways involving cytochrome P450. Aging is known to result in a general decrease in metabolic activity [Eap and Baumann 1996, Leinonen et al. 1996, Winston 1997]. However, the importance of gender arises because of the reduced rate of metabolism in females where cytochrome P450 1A2 and 3A4 are expressed to a lower degree and renal elimination is increased [Beierle et al. 1999, Eap and Baumann 1996].

There was no statistically relevant correlation between trazodone serum levels and dosage, body weight, smoking behavior, mono-, polypharmacy and treatment duration. Up to 80% of the patients received trazodone in a dosage range from 100 mg to 200 mg. Although dosages up to 450 mg of trazodone are recommended by the suppliers and may be necessary to produce adequate antidepressive efficacy, such dosages are rarely prescribed by us in our clinical routine (15.4%). We prefer using low-dose trazodone in a drug combination where the immediate effects of the drug on anxiety and sleep disturbance can be obtained and the hypotension side effect be avoided. Furthermore, in post-traumatic stress-, adjustment- and somatoform disorders where trazodone is given primarily as a support in psychotherapy, patients benefit from an improved sleep induction without hypnotic effects. With the combination strategy it is also possible to avoid dependence phenomena. None of the patients studied, experienced any of the expected adverse effects such as dizziness, severe headache, daytime sedation or fatigue. A serotonin syndrome, even in a mild form, did not occur [Sternbach 1991]. In contrast to our findings, Metz and Shader [1990] reported adverse in-

teractions when using low doses of trazodone (25 – 75 mg) together with fluoxetine to treat insomnia. Sixteen patients showed a good hypnotic response but 5 had to stop medication due to excessive sedation. In 1992, Nierenberg and colleagues presented a case series of patients taking fluoxetine who were given trazodone either for sleep or as a possible antidepressant potentiator. Three patients showed an improvement in both sleep and depression, the remaining 5 patients were either unaffected by the comedication or complained of sometimes intolerable adverse drug reactions.

Only few studies involving the simultaneous determination of 2 or more CNS drugs have been published [Eap and Baumann 1996, Waschgler et al. 2002]. Simultaneous analysis of several drugs not only decreases the costs and increases the speed of analysis, but is also useful when polypharmacy is indicated. Our results demonstrate the need for integrating analytical drug measurements into clinical assessments in order to guarantee safety in clinical polypharmacy and provide the means for individual dose adjustments [Dubovsky 1994, Markowitz 1997, Zapotoczky and Simhandl 1995].

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