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Neuroendocrine Effects of a 20-mg Citalopram Infusion in Healthy Males

A Placebo-Controlled Evaluation of Citalopram as 5-HT Function Probe

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Pharmacokinetic measurements, neuroendocrine responses, and side effect profiles of intravenous infusions of 20 mg citalopram over 30 minutes during the early afternoon have been studied. Eight healthy male volunteers were enrolled in a placebo- (saline) controlled, single-blind, cross-over protocol. Plasma concentrations of the parent compound showed a double exponential decay. Demethyl and didemethyl metabolites were not detectable, but low concentrations of the propionic acid derivative of citalopram were found. Determination of the citalopram enantiomers yielded a balanced S(+)/R(−) ratio of 0.9 to 1.2. The endocrine response to the drug was characterized by significant increases in plasma prolactin and cortisol. Except for one subject, who developed pronounced side effects, human growth hormone showed a surge following saline that was inhibited following citalopram. Rectal temperature and heart rate were not affected and tolerability was favorable. Because of citalopram's extremely high selectivity for the presynaptic 5-hydroxytryptamine nerve terminals, the present data suggest that it might be a promising tool for the investigation of serotonergic function in the human brain in vivo. ***[Neuropsychopharmacology 14:253–263, 1996]***

KEY WORDS: *Serotonin reuptake inhibitor; SSRI; 5-Hydroxytryptamine; 5-HT receptor probe; Pharmacokinetics; Enantioselectivity; Neuroendocrinology; Side effects; Cytochrome P-450*

Perhaps no other neurotransmitter system has received the attention afforded serotonin (5-hydroxytryptamine, 5-HT) in the pathophysiology and treatment of affective and other psychiatric disorders (Meltzer et al. 1984; Coccaro et al. 1989; Cowen et al. 1989; Kahn et al. 1990; Price et al. 1990; Delgado et al. 1991; Lesch et al. 1991; Asnis et al. 1992; Gillin et al. (in press); Hollander et al. 1994; Salomon et al. 1994; Cleare and Bond 1995).

Probes measuring hormonal secretion in response to serotonin precursors and agonists have provided valuable *in vivo* methods to assess the activity of serotonergic neurotransmission and serotonin receptor sensitivity (Maes and Meltzer 1995). However, several pitfalls of this strategy should be borne in mind. Bioavailability and metabolism may vary considerably between different drugs, subjects, and routes of administration (Golden et al. 1991). Furthermore, receptor specificity, affinity for pre- or postsynaptic 5-HT binding sites, and side effect profiles are other sources of variability of outcome mea-

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surements (Benkelfat 1993). In light of the rapidly growing number of characterized and cloned 5-HT receptor subtypes (Hoyer et al. 1994), specific probes are crucial for further *in vivo* research of their (patho)physiological function. For example, selective 5-HT_{1A} agonists (Cowen et al. 1990) such as ipsapirone have helped to elucidate this receptor's role in depression (Lesch et al. 1990; Meltzer and Maes 1995). However, there are few subtype specific agonists available for human use. Certain subtype probes have limited specificity. This makes it difficult to ascribe particular behavioral functions to particular receptors. Buspirone, for instance, a 5-HT_{1A} agonist, has also considerable affinity for dopaminergic neurons. Thus it turns out that this drug is less suitable as a 5-HT function probe (Meltzer and Maes 1994b). An alternative research strategy to disentangle 5-HT receptor subtype function comprises the application of probes stimulating all 5-HT neurons and then combining these probes with receptor subtype blockers. Though there are no ideal selective blockers available yet, the 5-HT_2 antagonists ritanserin (Charig et al. 1986) and ketanserin (Cowen and Anderson 1986) or the 5-HT_{1A} antagonist pindolol (Smith et al. 1991; Meltzer and Maes 1994a) are useful tools. Clomipramine, a relatively selective serotonin reuptake inhibitor with no known preference for particular 5-HT subtypes, has successfully been used as a subtype unspecific 5-HT stimulator (Laakmann et al. 1984; Anderson and Cowen 1986; Golden et al. 1989, 1990, 1992; Jarrett et al. 1991). However, the 5-HT specificity of this drug is limited. At least from a conceptual point of view, its weak affinity for noradrenergic neurons (Hall and Ogren 1981; Hyttel 1982) renders clomipramine less than entirely ideal. In addition, the major metabolite demethyl-clomipramine acts preferentially as a noradrenaline reuptake inhibitor (Carlsson et al. 1969).

Alternative compounds with higher selective actions at 5-HT synapses and better tolerability are needed for a more detailed *in vivo* investigation of central 5-HT function (Van Praag et al. 1987). Based on the following reasons, the second-generation antidepressant citalopram might be a candidate. Citalopram is the most selective serotonin reuptake inhibitor available at present and exhibits no known intrinsic activity at 5-HT or other receptor families (Milne and Goa 1991). This compound can be administered intravenously in doses up to 60 mg and is generally well tolerated in both depressed patients and normal controls (Itil et al. 1984; Lader et al. 1986; Charbonnier et al. 1987). Further evidence for a promising candidacy derives from preclinical studies. The acute administration of citalopram in the rat amplifies 5-hydroxytryptophan-induced prolactin secretion (Meltzer et al. 1981).

The objective of the present trial was to test the hypothesis that citalopram might be used as a neuroendocrine probe for the *in vivo* assessment of 5-HT function. We investigated the effects of intravenous infusions of 20 mg citalopram on the secretion of prolactin, cortisol, and human growth hormone, and on rectal temperature, heart rate, and side effect profiles in eight healthy male volunteers. Acute pharmacokinetic characteristics, including plasma concentrations of the parent compound, the metabolites, and the enantiomers, were determined.

MATERIALS AND METHODS

Subjects

Eight paid healthy male volunteers (university students; age range 22–29 years, mean ± standard deviation 24.3 ± 2.6 years) were enrolled. Written informed consent was obtained after explanation of the purpose and design of the study. The protocol was approved by the Ethics Committee for Human Experiments of the University of Basel according to the 1975 Helsinki Declaration. The study was carried out in the Depression Research Unit, Department of Psychiatry, Basel. All subjects underwent an extensive physical and laboratory check-up, including hematology, clinical chemistry, toxicologic urine probe, electroencephalogram (EEG), and electrocardiogram (ECG). An extensive semistructured interview was conducted to exclude any personal and family history of psychiatric disorder or stressful life events during the 3 months prior to the investigation. Further exclusion criteria were any physical or laboratory abnormalities, body mass index (BMI) <20 or >25 kg/m^2, habitual smoking, drug abuse, increased intake of alcohol (>25 g/d) or of caffeine (>500 ml coffee/d), shift work, any medical treatment, and participation in a biomedical experiment during the past 6 months. Intake of caffeine-containing beverages was allowed in the morning prior to the experimental session. Alcohol-containing drinks were not allowed for at least 4 days before the study. Subjects took their breakfast at home at about 0700 h.

Study Design

The randomized counterbalanced single-blind crossover protocol consisted of two experimental trials. Two additional trials included a sleep deprivation protocol (data not shown here). These did not interfere with the present study, and the possible sequence effects were ruled out appropriately. To prevent carry-over effects, all sessions were separated by at least 21 days. After carrying out their usual daily activities during the morning hours, subjects were admitted at 1130 h. Following the insertion of two intravenous cannulas, subjects took a standard lunch (600 kcal) consisting of equal parts of carbohydrates, proteins, and lipids between 1200 and 1230 h. Subjects remained at strict bed rest from 1200 h until termination of the procedure at 1700 h.

Napping was prohibited and controlled for by the laboratory staff. Room temperature ranged between 18 and 22°C, light intensity ranged between 200 and 400 lux.

To preserve highly standardized environmental conditions and to avoid stress effects due to manipulations at the catheter system, subjects remained alone in the bedroom (door closure at 1400 h). Video and a two-way audio communication system allowed continuous monitoring. Infusions and blood drawings were carried out using the through-the-wall technique as described elsewhere (Seifritz et al. 1995).

Neuroendocrine Procedure

Bilateral antecubital indwelling intravenous catheters were connected to a plastic tubing extension placed through a soundproof lock into the adjacent room. These extensions were kept patent with a constant 0.9% saline drip containing heparin. One cannula (Venflon®) that was connected with a IVAC-Star-Flow® was used for drawing blood samples. The other, a Butterfly23®, was used for placebo (0.9% saline; SAL) or citalopram (CIT; 20 mg citalopram hydrochloride concentrate diluted in 25 ml 0.9% saline) infusions. Constant-rate infusions (50 ml/h) of CIT or SAL were achieved using a Braun-Perfusor-Secura-FT®. CIT ampules were kindly provided by H. Lundbeck, Switzerland.

Blood samples were obtained at 1330 h, and from 1400 h onward at 20-min intervals until 1700 h. The samples from 1420 h were drawn just prior to the SAL or CIT infusion. To minimize possible postprandial and venipuncture stress effects, statistical analyses were performed on samples obtained from 1400 h onward. CIT and SAL were infused over 30 minutes beginning at 1420 h. The perfusor was stopped at 1450 h. The relatively slow 30-minute infusion was chosen for safety reasons and to comply with the Swiss drug registration council's recommendations.

Body Temperature

Rectal temperature was measured using a 100-mm thermistor probe (0.1°C resolution) that was connected to a 414-Dual-Pressure-OPT21® in the adjacent room. Values were recorded visually from a digital display at 10-minute intervals from 1400 h onward.

Heart Rate

Heart rate was monitored using an on-line ECG (414-Dual-Pressure-OPT21®) and recorded at 10-minute intervals.

Self-Report Scales

Visual 100-mm analogue scales (VAS) were completed by the subjects at 20-minute intervals. The following 13 items describing their subjective state were assessed: (1) Well-being (best/worst); (2) Mood (happy/sad); (3) Anxiety (none/severe); (4) Distress (relaxed/distressed); (5) Restlessness (calm/restless); (6) Alertness (energetic/tired); (7) Sickness (feeling comfortable/feeling sick); (8) Nausea (none/severe); (9) Dizziness (none/severe); (10) Tremor (none/severe); (11) Headache (none/severe); (12) Sweating (none/strong); and (13) Dry mouth (hypersalivation/dryness of the mouth).

Collection and Assay Techniques

After anticoagulation (CIT specimens: 20 IU heparin per ml; hormone specimens: 500 μg EDTA + 125 KIU trasylol per ml), the blood samples were centrifuged for 10 minutes at 4,000 g at 2°C and stored frozen at −80°C until assayed. Measurements of plasma concentrations of each individual were determined in the same assay.

Drug concentrations were assessed in the Unité de biochimie et psychopharmacologie clinique, Département Universitaire de Psychiatrie Adulte, Prilly-Lausanne. CIT and the metabolites demethyl-CIT (D-CIT) and didemethyl-CIT (DD-CIT) were determined by gas chromatography, and CIT-propionic acid derivative (CIT-PROP) by gas chromatography-mass spectrometry, respectively (Reymond et al. 1993). Lower quantitation limits, intra- and interassay coefficients of variation were: 1 ng/ml, 5.5% and 3.6% for CIT; 1 ng/ml, 5.4% and 4.5% for D-CIT; 2 ng/ml, 9.3% and 7.9% for DD-CIT; 2 ng/ml, 5.2% and 6.6% for CIT-PROP. S(+) and R(−) enantiomers of CIT in plasma samples obtained at 1440, 1520, and 1700 h were determined by a recently developed chiral reverse-phase liquid chromatography assay (Rochat et al. 1995) with a lower quantitation limit of 3 ng/ml and intra- and interassay coefficients of variation of 5.5% and 8.4%, respectively.

Plasma concentrations of prolactin (PRL), cortisol, and human growth hormone (hGH) were determined in the Max Planck Institute of Psychiatry, Munich, Germany, by commercial radioimmunoassay kits [Nichols Institute, San Juan Capistrano, CA, USA (PRL, hGH); ICN Biomedicals, Carson, CA, USA (cortisol)], with lower quantitation limits of 0.2 ng/ml for PRL and hGH, and 0.3 ng/ml for cortisol. Intra- and interassay coefficients of variation were under 8% for PRL and hGH [at 2 and 8 ng/ml (PRL) and 5 ng/ml (hGH) plasma levels] and under 7% for cortisol (at 20 and 40 ng/ml plasma levels), respectively.

Data Analysis and Statistics

Baseline values of hormones, temperature, heart rate, and VAS ratings were defined as the average of preinfusion values obtained between 1400 and 1420 h. Postinfusion responses in both conditions were expressed first as the maximum change (Δ_{max}) from baseline and sec-

ond as net area under curve (ΔAUC; trapezoidal integration corrected for baseline values; ng/ml*min). To analyze the dynamics of changes, data were aggregated to three time blocks: (1) baseline (1400–1420 h mean); (2) first postinfusion hour (1440–1540 h mean); and (3) second postinfusion hour (1600–1700 h mean).

Baseline, Δ_{max}, and ΔAUC values were compared using the Wilcoxon-signed ranks test (Z; SAL vs. CIT). Repeated-measures analysis of variance [ANOVA; 2 × 3 factorial design; Greenhouse-Geisser's Epsilon ($\hat{\epsilon}$) for adjustment of degrees of freedom] was employed to assess main effects of condition (SAL vs. CIT) and time (baseline, first hour, second hour), and the interaction of condition × time.

The emergence of side effects was defined as a Δ_{max} exceeding 20 mm on the VAS. Values between 20 and 50 mm were rated as mild, and values over 50 mm were rated as moderate to severe. Items with significant differences in Δ_{max} were further analyzed using ANOVA. Spearman rank correlations of Δ_{max} values were computed to estimate possible associations between self-report ratings and hormones, heart rate, and rectal temperature.

Values in the text are means and standard deviation. Level of significance was set at $\alpha = 0.05$ (trend level: $\alpha = 0.10$).

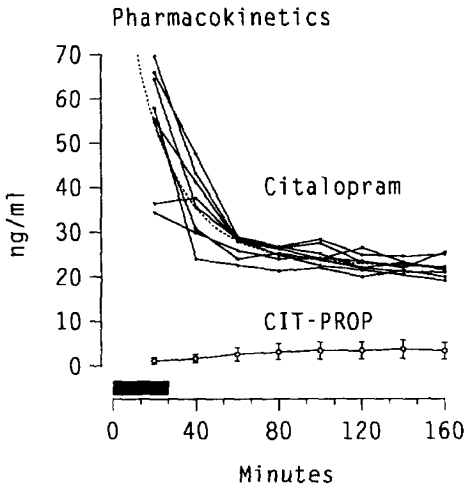

Figure 1. Time course of citalopram plasma concentration ($n = 8$) and citalopram-propionic acid derivative (CIT-PROP; $n = 4$, means and SEM). *Dotted line* represents curve fit using a double exponential decay function. Bar on top of abscissa denotes time of IV infusion of 20 mg citalopram.

RESULTS

Pharmacokinetics

Plasma concentrations of CIT following intravenous infusions are shown in Figure 1. The highest values (54.9 ± 12.8 ng/ml) were obtained at 1440 h, that is, 20 minutes after the start of infusion. Immediate decreases of initial concentrations by about 30% indicate a rapid distribution within the central compartment. From approximately 30 minutes after termination of infusion until 1700 h, plasma CIT concentrations remained rather constant (1520–1700 h mean: 23.9 ± 1.6 ng/ml). The time course appears to be best explained by a double exponential decay function curve fit. Graphical estimation was supported by an ANOVA that yielded no differences between raw and fitted values [interaction time × plasma concentration (raw vs. fitted): $F(7, 49) = 0.1$, $\hat{\epsilon} = .22$, $p = .830$].

The major metabolites D-CIT and DD-CIT were undetectable in all samples. CIT-PROP was found in very low concentrations [about 2%–20% of parent compound, range 1.0–5.2 ng/ml (determined in 4 subjects)]. Determination of CIT enantiomers three times in each subject yielded a mean ratio S(+)/R(−) CIT of 1.03 ± 0.09 (range: 0.9–1.2). This range was within the assay's coefficients of variation.

One out of eight subjects developed pronounced side effects. These would confound the interpretation of the "normal" endocrine responses. This outlier has therefore been omitted from the following statistical analyses and will be described separately and in detail.

Plasma Hormone Concentrations

Time courses of plasma hormone concentrations are illustrated in Figure 2. Baseline values of PRL, cortisol, and hGH did not differ between conditions (SAL/CIT condition: PRL 8.15 ± 3.31/8.81 ± 3.53; cortisol 93.53 ± 68.56/105.72 ± 58.65; hGH 0.56 ± 0.39/0.71 ± 0.47 ng/ml).

Following the CIT infusion mean PRL concentrations rapidly rose from baseline to maximum levels (17.80 ± 4.65 ng/ml) at 80 minutes after the start of infusion. Thereafter, PRL values continuously declined (1440–1700 h mean: 13.26 ± 2.72 ng/ml). PRL was not substantially affected by the SAL infusions, and the level remained quite constant (1440–1700 h mean: 9.12 ± 3.27 ng/ml; max: 12.10 ± 4.35 ng/ml). Comparison of integrated PRL net secretion (ΔAUC) showed significantly higher values in the CIT than in the SAL condition ($Z = -2.2$; $p = .028$). These differences were even more pronounced when the net AUC of the first postinfusion hour (1440–1540 h) was considered ($Z = -2.4$; $p = .018$). The ANOVA for the mean PRL plasma concentrations showed significant main effects for treatment and a significant interaction of treatment × time block [treatment: $F(1,6) = 9.1$, $p = .023$; time: $F(2,12) = 2.3$, $\hat{\epsilon} = .83$, $p = .151$; interaction: $F(2,12) = 6.3$, $\hat{\epsilon} = .54$, $p = .042$] (Figure 2, Panel 1).

Mean plasma cortisol concentrations during the SAL condition showed a declining trend from 1400 h onward (1600–1700 h mean: 54.70 ± 23.63 ng/ml). Follow-

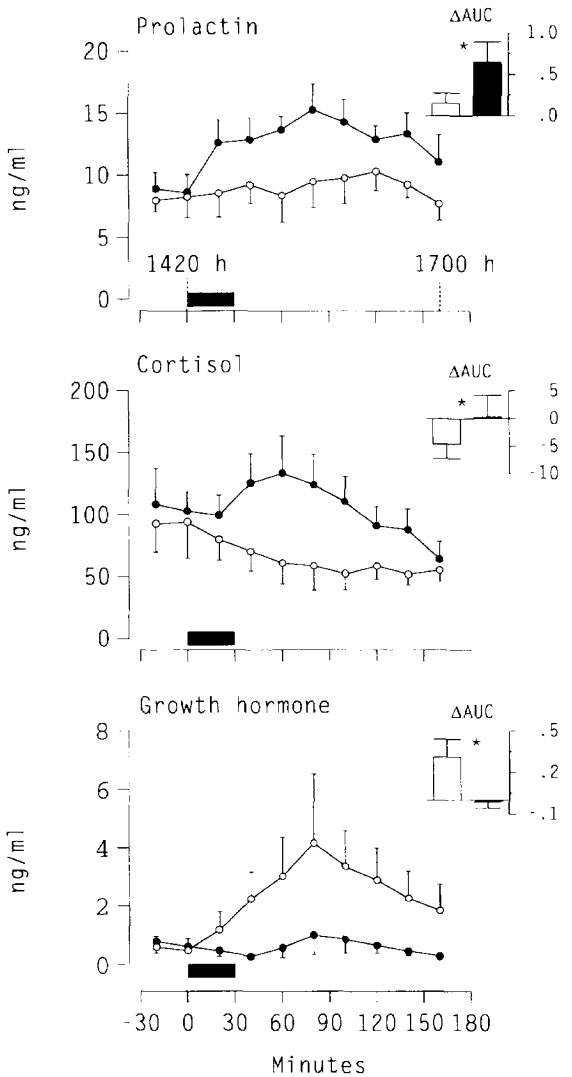

Figure 2. Time course of prolactin, cortisol, and growth hormone (n = 7, means and SEM). Bars on the top of abscissa denote time of citalopram or saline infusion. Inserts show net secretion [area under curve (ΔAUC) corrected for baseline] following infusion (*p < .05; Wilcoxon-signed ranks test). *Open circles* denote saline condition, *black circles* denote citalopram condition.

ing the CIT infusion, cortisol increased and reached a peak approximately 1 hour after the start of infusion (156.86 ± 62.33 ng/ml). There was a significantly larger ΔAUC in the CIT condition than in the SAL condition (z = −2.0; p = .043). The ANOVA yielded a significant main effect for treatment and a trend for an interaction of treatment × time block [treatment: $F(1,6)$ = 7.5, p = .033; time: $F(2,12)$ = 1.3, $\hat{\epsilon}$ = .54, p = .293; interaction: $F(2,12)$ = 4.2, $\hat{\epsilon}$ = .76, p = .060] (Figure 2, Panel 2).

An inverse picture was obtained for the response curves of hGH. In the SAL condition hGH showed significant increases from baseline onward (max: 6.63 ± 5.41 ng/ml); in the CIT condition hGH secretion was inhibited (max: 1.41 ± 1.68 ng/ml). Likewise ΔAUC following CIT was significantly decreased as compared to the SAL condition (Z = −1.99; p = .046), and the ANOVA revealed a significant main effect for treatment [treatment: $F(1,6)$ = 9.3, p = 0.23; time: $F(2,12)$ = 1.94, $\hat{\epsilon}$ = .91, p = .190; interaction: $F(2,12)$ = 1.9, $\hat{\epsilon}$ = .75, p = .205] (Figure 2, Panel 3).

Body Temperature

Rectal temperature was not affected by the experimental manipulations (Figure 3). There were no significant main and interaction effects.

Heart Rate

In both conditions heart rates showed a declining trend across time (Figure 3). This was substantiated by a significant main effect for time block [treatment: $F(1,6)$ = 1.6, p = 2.52; time: $F(2,12)$ = 6.9, $\hat{\epsilon}$ = .60, p = .033; interaction: $F(2,12)$ = .21, $\hat{\epsilon}$ = .88, p = .787].

Self-Report Scales

The subjects tolerated SAL and CIT infusions well. Significant increases in VAS Δ_{max} following CIT were found

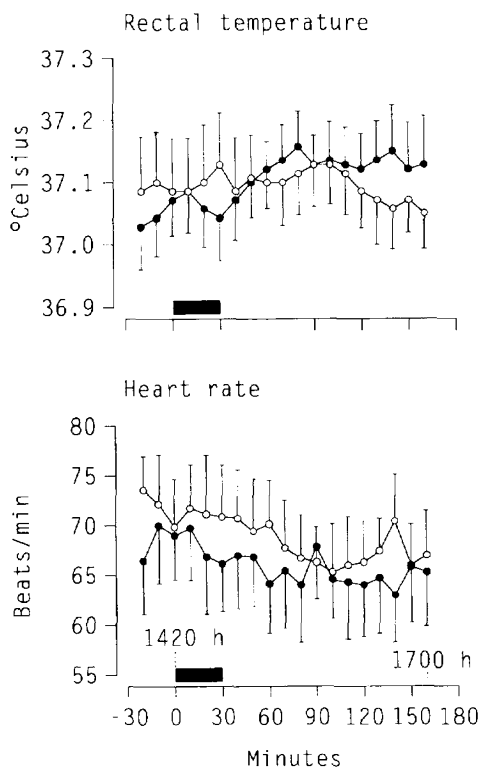

Figure 3. Time course of rectal temperature and heart rate (n = 7, means and SEM). *Black circles* denote citalopram condition, *open circles* denote saline condition. Bars on top of abscissa denote time of infusion.

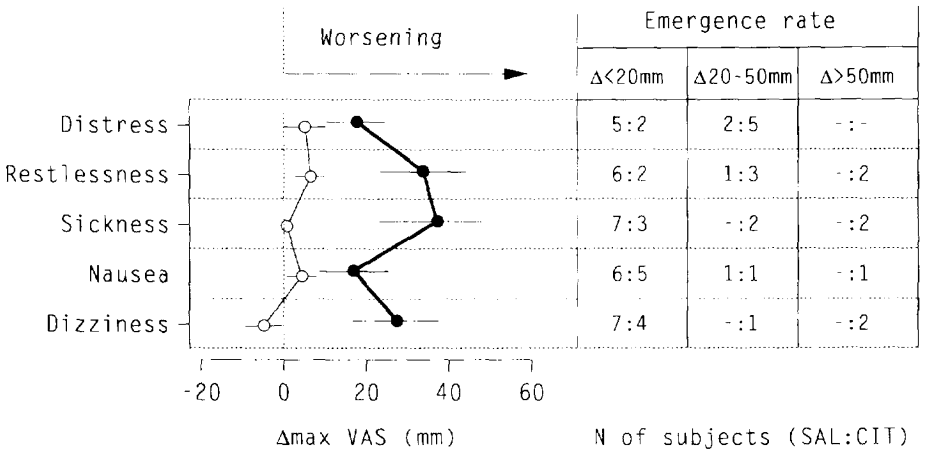

Figure 4. Changes and emergence rates of side effects. Values are means and SEM ($n = 7$) of peak changes (Δ_{max}) on 100-mm visual analogue scales (VAS). Only the items with significant differences between postcitalopram and postsaline Δ_{max} values are shown ($p < .05$, Wilcoxon-signed ranks test). *Black circles* indicate citalopram condition (CIT), *open circles* indicate saline condition (SAL). Table insert shows the number of subjects developing Δ_{max} values within respective ranges.

for the items Distress, Restlessness, Sickness, Nausea, and Dizziness (Figure 4).

An ANOVA of these items yielded a significant treatment × time block interaction and a trend for treatment main effect for the item Restlessness [treatment: $F(1,6) = 6.2$, $p = .051$; time: $F(2,12) = 3.8$, $\hat{\epsilon} = .96$, $p = .080$; interaction: $F(2,12) = 5.1$; $\hat{\epsilon} = .01$, $p = .036$]. A significant treatment effect was found for Sickness [treatment: $F(1,6) = 6.2$, $p = .047$; time: $F(2,12) = 3.8$, $\hat{\epsilon} = .64$, $p = .038$; interaction: $F(2,12) = 3.5$; $\hat{\epsilon} = .61$, $p = .098$]. The highest number of subjects exhibiting a Δ_{max} over 50 mm on the 100-mm VAS was two out of seven. Medical intervention or interruption of the protocol was not necessary, and none of the subjects vomited. Semi-structured interviews at the end of each trial revealed that the subjects rated side effects as well tolerable. It is noteworthy that the subject suffering from a Δ_{max} over 50 in the item Nausea following CIT also felt nauseated following SAL.

Correlations VAS Hormones

Spearman rank correlations between the Δ_{max} of hormone responses and of VAS scores yielded no significant correlations. Because of the small variance of drug concentrations, correlations with these values were not performed.

Outlier

One subject (age: 25 years, BMI: 25 kg/m^2) developed severe nausea (however without vomiting), sweating, flush, tremor, and peripheral paresthesia. Mental status changes did not occur. There were no differences in pharmacokinetic data compared with the other subjects (Figure 1). Hormone response following CIT was characterized by an exaggerated increase (Δ_{max}) in PRL (74.9 ng/ml), cortisol (329.6 ng/ml), and hGH (13.3 ng/ml). These increases all exceeded the upper 99% confidence interval (CI) for mean Δ_{max} values of the other seven subjects in the CIT condition (upper CI 99%: PRL, 16.94 ng/ml; cortisol, 166.10 ng/ml; hGH, 3.15 ng/ml). Rectal temperature transiently increased from 37°C at baseline to 37.5°C. Heart rate decreased transiently from 58 beats/minute at baseline to 46 beats/minute. All side effects were completely reversed within 2 hours and did not recur.

Several weeks after the trial to evaluate possible pharmacogenetic abnormalities in this subject, a combined dextromethorphan/mephenytoin test was performed. This test allows the determination of the phenotype of the liver cytochromes P-450IID6 and P-450$_{meph}$ (Baumann and Jonzier-Perey 1988; Baumann et al. 1992). The results yielded normal ("extensive") metabolism rates for both dextromethorphan and mephenytoin.

DISCUSSION

Intravenous infusions of 20 mg citalopram over 30 minutes led to consistent plasma concentrations of the parent compound, no demethylated metabolites, and a balanced S(+)/R(−) enantiomer ratio. The drug prompted an increase in plasma prolactin and cortisol and a decrease in growth hormone secretion. Tolerability was favorable in seven out of eight subjects.

Pharmacokinetic data are compatible with and extend previous findings. Demethylated metabolites of citalopram were not detected within the first 140 minutes after the start of infusion. However, the propionic acid derivative of citalopram was found in very low concentrations. Concentration curves of the parent compound yielded a time course that is compatible with an open two-compartment model and a reported plasma elimination half-life of 33 hours (Kragh-Sørensen et al. 1981). The pharmacodynamically active isomer of the

citalopram racemate, S(+) citalopram (Hyttel et al. 1992), was found in equal concentrations in all subjects. This indicates that there is no stereoselectivity during the acute metabolism phase. Interestingly, this finding is at variance with what has been found after long-term administration of citalopram in depressed patients (Rochat et al. 1995).

Citalopram exhibits highly selective serotonin reuptake-inhibiting properties at the presynaptic nerve terminal. The affinity for different receptors such as 5-$HT_{1A;1B;2}$, muscarinic, dopamine$_{1;2}$, $\alpha_{1;2}$, and $\beta_{1;2}$-adreno, histamine$_1$, benzodiazepine, opioid, and monoamine oxidase inhibitor receptors is very low (Hyttel 1982). Thus the neuroendocrine and behavioral responses to citalopram appear to be due to an increase of naturally occurring serotonin in the synaptic cleft.

The main and most robust endocrine finding in the present study was the transient surge of prolactin and cortisol following citalopram administration. The increase in plasma prolactin concentration following acute citalopram administration is in line with that found in animal studies (Meltzer et al. 1981). Considerable evidence has accumulated for a role of serotonergic pathways in controlling pituitary prolactin release. This hormone has become the target parameter in serotonergic probes (Power and Cowen 1992; Maes and Meltzer 1995). Animal studies indicate that serotonin-stimulated prolactin release is mediated through the dorsal raphe nucleus (Van de Kar and Bethea 1982) and the hypothalamic paraventricular nucleus (Minamitani et al. 1987). Destruction of afferent 5-HT neurons to the hypothalamus abolishes the prolactin response to 5-HT stimulation (Fessler et al. 1984). Intravenous administration of the 5-HT precursor L-tryptophan elevates prolactin (MacIndoe and Turkington 1973). This stimulation is enhanced by pretreatment with clomipramine (Anderson and Cowen 1986). Methysergide, a 5-HT receptor blocker, inhibits prolactin response to clomipramine (Laakmann et al. 1983). The administration of metergoline, a mixed 5-HT_1 and 5-HT_2 blocker, abolishes the endocrine responses to the postsynatic 5-HT agonist m-chlorophenylpiperazine (Mueller et al. 1986).

The 5-HT_1 receptor subtype has been suggested to play a key role in prolactin stimulation (Kellar et al. 1992). Ritanserin, 5-$HT_{2/1C}$ antagonist, does not block but rather enhances prolactin response to L-tryptophan (Charig et al. 1986). In addition, the 5-HT_{1A} agonists gepirone, buspirone (Cowen et al. 1990), and flesinoxan (Ansseau et al. 1992; Seletti et al. 1995), but not ipsapirone (Lesch et al. 1990; Kahn et al. 1994), lead to an increase in prolactin. Besides the 5-HT_{1A} receptor the 5-HT_{1B} (Van de Kar 1991) and 5-$HT_{1C/2}$ receptors (Jørgensen et al. 1992) also are involved in prolactin release. The central 5-HT_3 receptors, however, are not likely to play a role (Levy et al. 1993). The functions of the recently described 5-HT_{4-7} receptors are not yet clarified (Hoyer et al. 1994).

Stimulation of cortisol by 5-HT agonists appears less specifically mediated through 5-HT neuronal pathways (Van de Kar et al. 1985). However, the present results are consistent with the data reported for clomipramine (Golden et al. 1989).

Citalopram administration led to an inhibition of the growth hormone surge that occurred following saline administration. The lack of a growth hormone stimulation is in line with studies using clomipramine, fenfluramine, and m-chlorophenylpiperazine but is in contrast to studies using 5-hydroxytryptophan, L-tryptophan, gepirone, and buspirone (Power and Cowen 1992). These data underline the still-puzzling association between 5-HT neurons and growth hormone release (Tuomisto and Männistö 1985). Studies in humans and rats have shown that fenfluramine exerts inhibiting rather than stimulating effects on growth hormone release. Dopamine-induced growth hormone secretion is inhibited by fenfluramine, and arginine-induced growth hormone stimulation is not amplified by fenfluramine (Casanueva et al. 1984). This is also supported by the finding that metergoline did not inhibit L-tryptophan-stimulated growth hormone release (McCance et al. 1988). It is very unlikely that effects other than the drug, such as admission, lunch, or venipuncture would have led to the different hormone responses. Such effects have been minimized as much as possible. The experimental setting has been held constant in both the citalopram and the saline conditions.

The question therefore arises of why growth hormone increased during the saline condition. Falling asleep or even the occurrence of slow-wave sleep, which are potent growth hormone stimulators (Born et al. 1988), can be ruled out with reasonable certainty. However, polygraphic data would be of interest to assess possible associations between EEG power spectra and the occurrence of growth hormone bursts. Among potential factors might be the quiescent sitting posture in bed and the absence of active social interaction. A study by Steiger et al. (1987) has shown that nocturnal growth hormone bursts in normal subjects may occur as early as 1 hour before sleep initiation when quiet bed rest is allowed. Similar results were obtained in another study measuring hormone profiles during daytime wakefulness in normal subjects (Wetzel et al. 1994). These authors reported that growth hormone peaks were most accentuated during the afternoon hours. Environmental- and arousal-associated stimulation of growth hormone needs further investigation. However, the present study documents an inhibition of growth hormone by the acute administration of citalopram.

Side effects appear to be intimately associated with acute 5-HT stimulation. These might bias the outcome measurements to a certain extent (Benkelfat 1993). However, analysis of the self-report questionnaires of seven subjects yielded a favorable side effect profile with 20

mg citalopram. These were not correlated with hormone levels. The severity of side effects was comparable with that reported for 10 to 25 mg clomipramine (Laakmann et al. 1984; Golden et al. 1989). Only the self-report item Restlessness showed a significant interaction of treatment × time in the analysis of variance. This might be in line with data documenting alerting effects of fluoxetine (Nicholson and Pascoe 1988). Such effects, however, still appear equivocal (Rammseyer and Netter 1988). Though not statistically correlated, Restlessness might be associated with the inhibition of growth hormone secretion during the citalopram trial.

The single subject who exhibited pronounced side effects showed an exaggerated increase in growth hormone (as opposite to the other subjects), in prolactin and cortisol, and an acute decrease in heart rate following citalopram. Because of the putative relationships between liver and brain cytochromes P-450 (Ross 1991), this subject was phenotyped using the combined dextromethorphan/mephenytoin test (Baumann and Jonzier-Perey 1988; Baumann et al. 1992). This examination, however, did not yield any pharmacogenetic abnormalities. So far, no conclusive pathophysiological explanation may be provided. However, it should be borne in mind that such side effects are quite frequent (Benkelfat 1993). This yet-unexplained idiosyncratic hypersensitivity of the 5-HT system—apparently found in a subgroup of the healthy population—awaits further clarification. In prevous studies using clomipramine in various doses, approximately 10% of the healthy subjects developed marked side effects, including severe nausea and vomiting (Laakmann et al. 1984; Golden et al. 1989).

For the interpretation of the hormone data, circadian mechanisms should be taken into account. The majority of previous studies placed the neuroendocrine testing in the morning hours. In contrast, the present experiment was performed during the afternoon. The ultradian variation of plasma prolactin and cortisol in humans shows a relatively stable downward trend during the afternoon hours (Linkowski et al. 1994). In the morning hours, on the other hand, the hypothalamic pituitary-adrenocortical and lactotrophic systems are relatively active (Van Cauter and Refetoff 1985). Furthermore, there is evidence for a circadian (Wesemann et al. 1986a; Wirz-Justice 1987) and vigilance state-associated (Wesemann et al. 1986b) variability in 5-HT neuron function. In this context recent findings by Jarrett and colleagues (1991) are of interest. These authors reported that the administration of clomipramine prompted a substantial increase in the sleep onset-associated growth hormone surge.

In summary the present study shows that a 20-mg citalopram infusion induces a robust, but moderate, hormone response in healthy male subjects. The most pronounced response is found in prolactin secretion during the first postinfusion hour. The occurrence of less specific metabolites as well as of an unbalanced ratio of the drug's isomers have been ruled out. The prolactin response appears to be due to a rapid and selective increase of endogenous transmitters in the synaptic cleft of 5-HT neurons in the brain. Therefore, it is surmised that citalopram might represent a promising tool for the neuroendocrine investigation of 5-HT function *in vivo*. Provided the validation of the hormone stimulation in dose-response relationship studies, the neuroendocrine and pharmacokinetic profile suggests that citalopram might be particularly useful in combination with 5-HT receptor subtype specific antagonists.

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