BRIEF REPORT

Usefulness of serotoninergic challenge with oral citalopram

Utilidade do desafio serotoninérgico com citalopram oral

Paulo Mattos,[1] Vanessa A Franco,[1] François Noel,[2,3] Daniel Segenreich,[1] José Carlos Gonçalves[3,4]

Abstract

Objective: Challenge tests designed to evaluate serotoninergic pathways have widely used intravenous citalopram. Oral citalopram has also been used, but unsatisfactory results were obtained with a dose of 20 mg. The objective of this study was to determine whether a higher oral dose would reproduce similar to those described for intravenous administration. To that end, we evaluated cortisol, growth hormone and prolactin levels. Method: Eight healthy male volunteers were evaluated in a randomized crossover challenge test with 40 mg of oral citalopram or placebo. Results: Cortisol levels increased at 2-4h after the oral citalopram intake, with a small amplitude peak occurring in two-thirds of the subjects. Levels of prolactin and growth hormone remained unchanged throughout the study. Conclusion: The use of oral citalopram might present an alternative in serotoninergic challenge tests, but higher doses are required.

Keywords: Citalopram; Cortisol; Prolactin; GH; Challenge

Resumo

Objetivo: Testes-desafio desenvolvidos para avaliar as vias serotoninérgicas utilizaram amplamente citalopram intravenoso. Citalopram oral também foi utilizado, mas obtiveram-se resultados insatisfatórios com uma dose de 20 mg. O objetivo deste estudo foi o de determinar se uma dose oral mais elevada poderia reproduzir resultados similares aos descritos para administração intravenosa. Com esta finalidade, avaliamos os níveis de cortisol, de hormônio do crescimento e de prolactina. Método: Oito voluntários do sexo masculino saudáveis foram avaliados em um teste-desafio cruzado, aleatorizado, com 40 mg de citalopram oral ou placebo. Resultados: Os níveis de cortisol aumentaram após 2-4 horas da ingestão de citalopram oral, com um pequeno pico de amplitude ocorrendo em dois terços dos indivíduos. Os níveis de prolactina e de hormônio de crescimento permaneceram inalterados ao longo do estudo. Conclusão: O uso de citalopram oral poderia apresentar uma alternativa em testes-desafio serotoninérgicos, mas doses maiores são necessárias.

Descritores: Citalopram; Cortisol; Prolactina; GH; Desafio

[1] Psychiatry Institute, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro (RJ), Brazil
[2] Institute of Biomedical Sciences, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro (RJ), Brazil
[3] Biopharmacy and Pharmacometry Program, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro (RJ), Brazil
[4] School of Pharmacy, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro (RJ), Brazil

Financing: This study was fully sponsored by the authors, except for the internal standards for citalopram and bromazepam and also citalopram tablets, which were provided by Lundbeck and Laboratórios Biosintética Ltda without any charges.
Conflict of interests: Paulo Mattos is either a speaker or a member of the advisory board of Wyeth, Novartis, Janssen-Cilag and Eli Lilly. He is recipient of a grant from NIMH (R01 MH65163-01). Daniel Segenreich is a speaker of Janssen-Cilag.
Submitted: 4 November 2005
Accepted: 25 May 2006

Correspondence
Paulo Mattos
Rua Paulo Barreto, 91
22280-010 Rio de Janeiro, RJ, Brazil
E-mail: paulomattos@mandic.com.br

Introduction

Challenge tests to evaluate serotoninergic function in psychiatric disorders[1-4] are common and usually evaluate corticotrophin-releasing hormone,[5-6] growth hormone[7] and prolactin.[8-9] Fenfluramine has given way to other agents, including 5-HT reuptake inhibitors (SSRI antidepressants). Although paroxetine has been used in challenge tests, citalopram is often the SSRI of choice due to its higher selectivity. In the only double-blind randomized study addressing 5-HT-mediated neuroendocrine response, no difference was found between citalopram, a racemic compound, and escitalopram,[10] its active isomer. Pharmacokinetic studies have shown that maximum plasma levels of approximately 130-160 nmol/l are generally obtained within 2-4 h after a 50-mg oral dose. A second, lower, peak is sometimes observed. The decline is considered to be monoexponential with a $t_{1/2}$ of approximately 30 h. Although intravenous citalopram has previously been used in serotoninergic challenge tests, this formulation is not available in many countries, and the only challenge test with oral citalopram (at a dose of 20 mg) produced less than satisfactory results. The objectives of this study were: 1) to measure plasma levels of cortisol, growth hormone and prolactin as a means of evaluating the neuroendocrine response to a higher dose (40 mg) of oral citalopram used as a tool to stimulate hormone secretion in neuroendocrine challenge paradigms; 2) to compare the kinetics of serum citalopram levels and neuroendocrine response using this higher dose of citalopram.

Method

Eight healthy male volunteers aged 18 to 48 years (mean 29.4 years) were actively recruited from among relatives of the medical and nursing staff of the hospital. The participants gave written informed consent and received financial compensation (minimum wage). Only men were recruited because of non-serotoninergic modulatory influences on female neuroendocrine response.[11] None of the volunteers had any history of psychiatric disorders. Nevertheless, all were interviewed, in an unstructured fashion, by a trained psychiatrist (PM). The results of the physical examinations and regular blood tests (blood counts, as well as for glucose, alanine aminotransferase, aspartate aminotransferase, creatinine and electrolytes) were normal and body mass indices were all within the normal range. Subjects were admitted to the hospital in the afternoon (17:00 h) of the day preceding the challenge test and were prohibited from smoking and drinking beverages with caffeine. Dinner (18:00 h) and supper (21:00 h) were prepared according to a special diet.[12] A forearm vein was used for the insertion of an intravenous cannula, and a saline infusion was initiated at 8:00 h. The first (baseline) blood sample was collected 15 min after the vein puncture. The subjects then received either 40 mg of oral citalopram or a placebo, both with 200 ml of water, in a crossover single-blind fashion. All volunteers underwent the challenge test first with the placebo and then with citalopram 6 months later.

Breakfast was served 15 min after intake. Subjects remained in bed for the duration of the 9-h test. A 2500-calorie lunch was served 5 h after citalopram or placebo intake, and a snack was served 3 h after lunch. Blood samples were collected through the cannula at different times during the day in order to determine plasma levels of citalopram (at 30, 45, 60, 90, 120, 180, 240, 300, 360 and 480 min), as well as of prolactin, cortisol and growth hormone (at baseline, 30, 60, 120, 240, 360 and 480 min). Chemiluminescence was used to perform the hormone analysis, Immulite (Diagnostic Products Corporation, Los Angeles, CA) to determine growth hormone levels, and ACS-Plus (Chiron Diagnostics, Emeryville, CA, USA) to determine levels of prolactin and cortisol. All analyses were carried out using dedicated kits. Citalopram levels were measured at the Federal University of Rio de Janeiro. Lundbeck laboratories (Paris, France) provided the citalopram tablets (batch No. A926), as well as the internal standard for the pharmacokinetic analysis. Bromazepam was used as internal standard and was supplied by Laboratórios Biosintética Ltda. (São Paulo, Brazil). The solid phase extraction was performed on a Prospekt 2 system (Spark Holland, Emmen, The Netherlands) with an automated cartridge exchange and a high-pressure dispenser. The cartridge was a HySphere C18 (15 × 2 mm I.D., 40-90 μm particles). We used an automated low-pressure Shimadzu gradient system with an LC-10ADvp solvent delivery, a DGU-10B degasser, an SCL-10Avp system controller and a CTO-10Acvp column oven (Shimadzu, Kyoto, Japan). The pre-column and column (150 × 4.6 mm I.D., 5 μm particles) were Shim-pack CLC-C8 (Shimadzu). Analysis was performed on a triple stage quadrupole Micromass QUATTRO LC system with an ESI interface (Waters, Milford, MA, USA). The ion transitions were monitored for bromazepam (m/z 316→182) and citalopram (m/z 325 →226).

Results

The plasma concentration of citalopram showed a small, poorly-defined, peak at approximately 1 h (45-120 min) after drug intake, ranging from 13.1 to 27.9 μg/ml in all subjects, except in one who presented an unexpectedly high peak (75.6 μg/ml) at 45 min after citalopram intake. After the initial peak, the citalopram concentration remained quite stable (approximately 15-20 μg/ml) until the end of the study, 8 h after drug intake. No side effects other than nausea (in two subjects) were reported.

The comparison of hormonal levels after placebo challenge (first phase) and citalopram (second phase) was performed in only six subjects, because two individuals from the original sample moved to another city. In all subjects, cortisol levels decayed progressively after placebo intake (Figure 1), and the same general pattern of progressive decline was apparent in the citalopram group. However, at 2-4 h after citalopram intake, cortisol levels increased in four of the six subjects, leading to a clear, small amplitude peak apparently "grafted" onto the declining curve (Figure 1).

Growth hormone levels increased in three of the four subjects who presented a rise in cortisol level and a peak at 2-3 h after citalopram intake. Curiously, the three subjects who did not present an increase in growth hormone levels after citalopram intake actually a peak at 2-3 h after placebo intake. The reason for this is unknown.

In two of the six subjects, prolactin levels increased after citalopram challenge. All measurements were within the normal range, except for that of one subject who had a baseline prolactin level above the upper normal limit, which might have been related to stress or even to a normally occurring pulse outside normal limits.[13]

Conclusion

The kinetics of the citalopram serum levels exhibited a pattern similar to what has been previously described, although the time to peak after oral administration was somewhat shorter

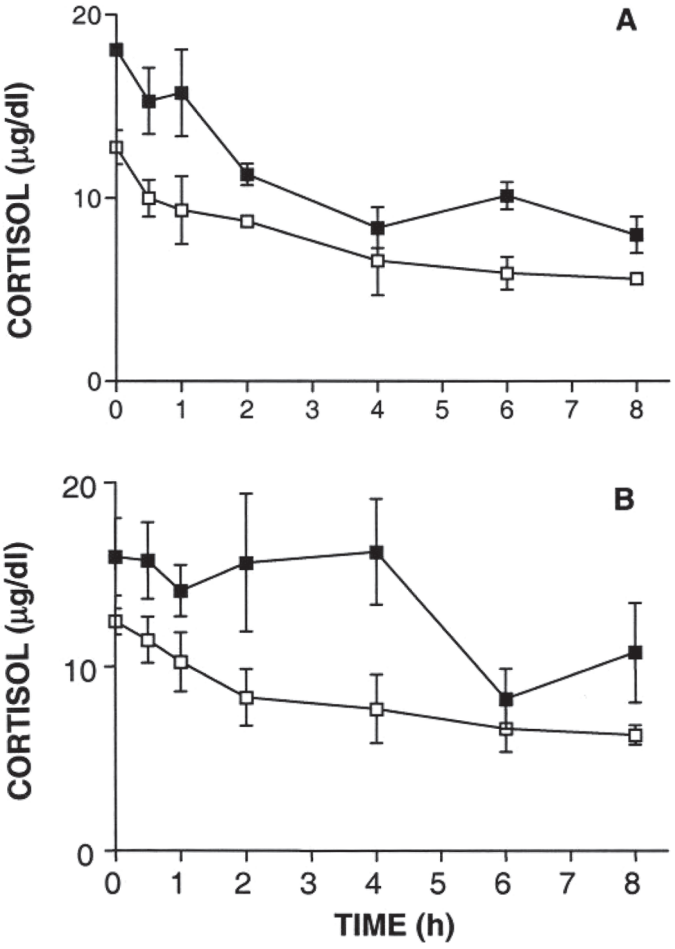

Figure 1 - Plasma levels of cortisol. Mean cortisol levels (+SEM) of volunteers 4 and 7 (A) and volunteers 5, 6, 8 and 9 (B) after placebo (□) or an oral dose of 40 mg citalopram (■).

in our study (45-120 min) than the 2-4 h typically reported. The small peaks in cortisol levels observed in four of the six subjects treated with citalopram could be considered a positive response to the serotoninergic challenge. The elevation of cortisol levels in these four subjects, observed between 10:15 am and 12:15 pm (2 h and 3 h after drug intake, respectively), was, physiologically speaking, unexpected, since cortisol levels typically peak between 7 and 9 am, declining during the late morning and afternoon, and reach their nadir between 11 pm and 3 am.[14]

Growth hormone levels increased at 2-3 h after intake in half of the subjects receiving citalopram and half of the subjects receiving the placebo, all increases occurring at the same time of day. These increases were therefore considered unrelated to the serotoninergic challenge.

Prolactin levels increased after citalopram challenge in two of the subjects, in contrast with the total absence of prolactin increases in another study involving a lower dose of oral citalopram.[15] However, prolactin has been reported to increase after the administration of 20 mg of intravenous citalopram.[7] One possible explanation might be that a rapid infusion or a higher dose is necessary to induce the release of prolactin.

Cortisol levels increased at 2-4 h after oral 40 mg citalopram challenge in most subjects. The results of the assessment of prolactin and growth hormone levels were considered negative. Despite the small sample size, the positive results obtained with a higher dose of oral citalopram in the present study prompts further investigation with larger series or different challenge designs.

References

1. Aberg-Wistedt A, Hasselmark L, Stain-Malmgren R, Aperia B, Kjellman BF, Mathe AA. Serotoninergic vulnerability in affective disorder: a study of the tryptophan depletion test and relationships between peripheral and central serotonin indexes in citalopram-responders. *Acta Psychiatr Scand*. 1998;97(5):374-80.
2. Stoff DM, Pasatiempo AP, Yeung J, Cooper TB, Bridger WH, Rabinovich H. Neuroendocrine responses to challenge with dl-fenfluramine agression in disruptive behaviour disorders of children and adolescents. *Psychiatry Res*. 1992;43(3):263-76.
3. Snoek-Heddek A, Van-Goosen SH, Matthys W, Sigling HO, Koppeschaar HP, Westenberg HG, Van Engeland H. Serotoninergic functioning in children with oppositional defiant disorder: a sumatriptan challenge study. *Biol Psychiatry.* 2002;51(4):319-25.
4. Dolan M, Anderson IM, Deakin JF. Relationship between 5-HT function and impulsivity and aggression in male offenders with personality disorders. *Br J Psychiatry*. 2001;178:352-9.
5. Hanley NR, Van de Kar LD. Serotonin and the neuroendocrine regulation of the hypothalamic-pituitary adrenal axis in health and disease. *Vitam Horm*. 2003;66:189-255.
6. Van de Kar LD, Urban JH, Richardson KD, Bethea CL. Pharmacological studies on the serotoninergic and non-serotonin-mediated stimulation of prolactin and corticosterone secretion by fenfluramine. Effects of pre-treatment with fluoxetine, indalpine, PCPA, and L-tryptophan. *Neuroendocrinology*. 1985;41:283-8.
7. Seifritz E, Baumann P, Muller MJ, Annen O, Amey M, Hemmeter U, Hatzinger M, Chardon F, Holsboer-Trachsler E. Neuroendocrine Effects of a 20-mg Citalopram Infusion in Healthy Males. *Neuropsychopharmacology* 1996;14(4):253-63.
8. Attenburrow MJ, Mitter PR, Whale R, Terao T, Cowen PJ. Low-dose Citalopram as a 5-HT neuroendocrine probe. *Psychopharmacology (Berl).* 2001;155(3):323-6.
9. Mueller EA, Murphy DL, Sunderland T. Further studies of the putative serotonin agonist, m-chlorophenylpiperazine: evidence for a serotonin receptor mediated mechanism of action in humans. *Psychopharmacology (Berl)*. 1986;89(3):388-91.
10. Nadeem HS, Attenburrow Mj, Cowen PJ. Comparison of the effects of citalopram and escitalopram on 5-HT mediated neuroendocrine response. *Neuropsychopharmacology.* 2004;29(9):1699-703.
11. McBride PA, Tierney H, DeMeo M, Chen JS, Mann JJ. Effects of age and gender on CNS serotoninergic responsivity in normal adults. *Biol Psychiatry.* 1990;27(10):1143-55.
12. Benton D. Carbohydrate ingestion, blood glucose and mood. *Neuroscience Biobehav Rev.* 2002;26(3):293-308.
13. Melmed S, Kleinberg D. Anterior Pituitary. In: Larsen PR, Kronenberg HM, Melmed S, Polansky KS, eds. *Williams Textbook of Endocrinology.* New York: Saunders; 2003. p. 177-279.
14. van Cauter E, Leproult R, Kupfer DJ. Effects of gender and age on the levels and circadian rhythmicity of plasma cortisol. *J Clin Endocrinol Metab.* 1996;81(7):2468-73.
15. Hennig J, Netter P. Oral application of citalopram (20 mg) and its usefulness for neuroendocrine challenge tests. *Int J Neuropsychopharmacology.* 2002;5(1):67-71.