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Therapeutic monitoring of escitalopram by dexamethasone suppression test

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Introduction. Depression is associated with a dysfunction of regulation of the hypothalamic-pituitary-adrenal, HPA, which is reflected in the alteration of the dexamethasone suppression test, DST.

Escitalopram and other SSRIs decrease the HPA axis response to the DST, beeing the aim of this study validate the DST as a surrogate marker of central serotonergic activity in the treatment with escitalopram and its application to the calculation of the dosage regimens.

Methodology. Prospective observational study on 29 patients, upon whom was performed the DST-test with 0.25 mg of Dexamethasone and subsequent genetic analysis of CYP2C19 by Progenika PHARMAchip test.

Results. The range of plasma cortisol levels post-DTS associated with each phenotypic group were: PM phenotype= 0.6 to 1.7 mcg/dl, IM phenotype= 1.2 to 3.5 mcg/dl and EM phenotype = 4.8 to 13.2 mcg/dl, being carried out the dose titration and correspondng, respectively, the following dose regimens: 3-4 mg/day, 5-8 mg/day and 10-31 mg/day.

Coclusiones. It has been shown that the DST test can be used as a surrogate marker of drug response to escitalopram and as a tool for dose adjustment, providing significant data on different phenotypes of CYP2C19 metabolizers.

Key words: Escitalopram, Cortisol, DST-test, CYP450, polymorphisms, Genotype, Phenotype

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Monitorización terapéutica de escitalopram mediante el test de supresión con dexametasona

Introducción. La depresión está asociada a una disfunción de la regulación del eje hipotálamo-pituitario-adrenal, HPA, que se refleja en la alteración del test de supresión con Dexametasona, DST.

Escitalopram y otros ISRS disminuyen la respuesta del eje HPA en el DST, siendo el objetivo del presente trabajo la validación del DST como marcador subrogado de la actividad serotoninergica central en los tratamientos con escitalopram y su aplicación al cálculo de sus regimenes nosológicos.

Metodología. Estudio prospectivo observacional sobre 29 pacientes, a los que se realizo el DST con 0,25 mg de Dexametasona y posterior análisis genético del CYP2C19 mediante test PHARMAchip de Progenika.

Resultados. El rango de valores de cortisol plasmático post-DTS asociados a cada grupo fenotipico fueron: fenotipo PM=0,6-1,7 mcg/dl, fenotipo IM=1,2-3,5 mcg/dl y para el fenotipo EM=4,8-13,2 mcg/dl, realizándose el ajuste nosológico y correspondiéndoles, respectivamente, las siguiente dosis: 3-4 mg/día, 5-8 mg/día y 10-31 mg/día.

Conclusiones. Se ha comprobado que el DST test puede utilizarse como marcador subrogado de la respuesta farmacológica al escitalopram y como instrumento para su ajuste nosológico, proporcionando datos significativos sobre distintos fenotipos metabolizadores del CYP2C19.

Palabras clave: Escitalopram, Cortisol, DST-test, CYP450, Polimorfismo, Genotipo, Fenotipo

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INTRODUCTION

Depression is a pathological alteration of the mood state, major depressive disorder being that studied most with a 10-25% prevalence. Its origin is complex, it being attributed to a deficient transmission of serotonin,

norepinephrine and dopamine associated to dysfunction of the hypothalamic-pituitary-adrenal axis regulation that is reflected in the Dexamethasone suppression test (DST) alteration.[1-4]

The decrease of serotoninergic transmission in the brain and the elevated secretion of cortisol presented by patients with major depression have achieved the category of axiom in the text books, cortisol being the key biological mediator through which the brain decreases serotoninergic transmission, causing depression in vulnerable persons.[5]

The role of serotonin in the stimulation of the HPA axis includes the effect on the Corticotropin-releasing hormone (CRH) by activation of the 5-HT1A and 5-HT2/5-HT1C receptors, modifying the negative feedback exerted by the glucocorticoids on the functionality of the HPA axis. The increase of CRH stimulates the HPA axis activity and increases the levels of glucocorticoids, responsible for the subsequent down-regulation of the glucocorticoid receptor (GR) or mineralocorticoids receptors (MR), and the deficient post-synaptic signaling of the serotonergic pathways that pass through the 5-HT1A receptor and the up-regulation of the 5-HT2 receptors.[6]

Therefore, as the reduction of the serotoninergic transmission is a well-known characteristic of depression, it is not surprising that the SSRIs constitute a clinically effective therapy to normalize HPA axis activity and that it is the first line of pharmacological treatment of depressive disorders. In this way, escitalopram and other SSRIs decrease the response of the HPA axis in the dexamethasone suppression test (DST), their plasma levels having a dose-dependent correlation with the decrease of post-DST plasma cortisol. Thus, this can be used as a biomarker for the calculation of the posological regimes of the antidepressive drugs whose principal action is activation of the serotoninergic transmission that regulates the HPA axis.[7-16]

Therefore, this study has aimed to validate DST as a surrogate marker to quantify the increase of central serotonergic activity induced by treatment with escitalopram and its subsequent application to the calculation of nosological regimes.

METHODOLOGY

Sample

An observational, prospective study was performed on 29 randomly chosen outpatients from among those of the consultation of our Mental Health Unit to validate the utility of DST in the usual clinical practice as a surrogate marker of central serotonergic activity induced by the treatment with escitalopram. All of them were receiving antidepressive treatment with Escitalopram (mean: 17.1±4.1 mg, range: 10-30 mg) for at least 4 weeks. Of these, 89.9%, n=26, were being treated with a single antidepressant (Escitalopram) and the remaining 10.1%, n=3, with two antidepressants (Escitalopram and Mirtazapine); 71.1%, n=21 were taking anxiolytics (benzodiazepines) and 14% more, n=4, of the patients were receiving treatment with Omeprazole (IBP).

A total of 90% of the subjects of the sample were women, mean age of 60.7±14.1 years (range=33-86). Of these, 17% were over 80 year, 28% between 65-80 year and the remaining 65% were younger than 65 years. According to the ICD-10 of dysthymia, the subjects had been diagnosed of F34, 35% (n=10), mixed anxiety-depressive disorder, F41, 48% (n=14) and the remaining 17% (n=5) with other depressive disorders. All the types of affective disorder, comorbidities and symptoms presented by the patients included in the sample, such as: dysthymia, anxiety, bipolar disorder, insomnia, post-traumatic stress, ADHD, major depression, burnout, chronic fatigue syndrome, fibromyalgia, alcoholism, etc.,[17] according to the bibliographic data consulted, had alteration of the HPA axis, the antidepressants routinely prescribed being able to regulate the HPA axis function.[18]

Performance of DST test

All the patients underwent the DST by means of a single nighttime dose (10 p.m.) of 0.25 mg dexamethasone followed by measurement of plasma cortisol (CORT) the next day (8 a.m.). In this test, the increase of the Dexamethasone dose used produces a dose-dependent decrease of the plasma levels of cortisol, causing suppression of them in most of the patients (more than 90%) with doses equal to or less than 0.5 mg.[19] It was decided to perform the DST test with 0.25 mg of Dexamethasone because the amplitude of the range of plasma cortisol values obtained with it is maximum compared to higher or lower doses. Thus, the levels of cortisol obtained are often below the limit of detection of the analytic technique. On the other hand, the post-PST cortisol levels obtained did not vary with gender, age, diagnosis, height, BMI, or severity of the symptoms. Therefore, said factors did not affect the validation process of the DST test on the sample chosen.[20]

Statistical study

The Kernel Test was used for the population analysis, carrying out the subsequent analysis of statistical significant using the Student's T test.

The Gaussian kernel test for the population analysis allows us to identify the populations with different phenotypes that make up the sample. To do so, a Gaussian function was associated to each experimental value of

$$f(x)=\frac{1}{2\pi\sqrt{h^2}}\,e^{1/2(d/h)^2}$$

Figure 1 | *Gaussian function used in the Kernel Test*

Cortisol in accordance with that shown in Figure 1. Thus, the horizontal axis (X) represents each one of the post-DST Cortisol values obtained with an equi-effective dose of Escitalopram (theoretical dose with which we would obtain a post-DST cortisolemia of 10 mcg/dl for each one of the patients). The vertical axis (Y) represents the intensity or frequency corresponding to each one of the Cortisol values. The final curve obtained is the sum of the Gaussian curves corresponding to each experimental value, its maximum values coinciding with those in which the frequency is higher, this decreasing parallelly with the frequency of each one of the cortisol values.

In the Gaussian curve applied, the mean (μ) was replaced by **d** which is the distance from a certain value of CORT to any other point on the x axis, and the variance (σ^2) by **h** which is the "band width," both expressed in mcg/dL.

The band width to be used depends on the type of analysis that is being done and implies a trial and error procedure until approaching the grade of resolution desired. In our case, that used was equal to 10, according to the following expression:

h = 1.06 x S x $N^{-0.2}$ (N = no. data and S=SD), **h = 10**

Pharmacogenetic analysis of CYP2C19 and SLC644A

Escitalopram is metabolized principally by CYP2C19 to demethylated metabolites of much lower pharmacological strength, the AUC of Escitalopram being directly and significantly correlated with the genotype present in each individual. The effect of the CYP2C19 genotype on the escitalopram dose is also seen by the different concentration/dose and drug/metabolite indexes as well as by the serum concentration presented by the individuals who are carriers of the defective alleles 2 and/or 3 of CYP2C19 versus those who carry active alleles (*).

Since the CYP2C19 genotype is probably the principal predictive factor of the metabolism of escitalopram and therefore of its concentration in plasma and/or biophase, a genotyping of the samples was made, after informed consent of the patient, using the PHARMAchip® test of PROGENIKA. This analyzed the presence or not of the defective alleles 2 and 3, whose combinations may explain the presence of almost 100% of the phenotypes "Poor Metabolizer" (PM) and "Intermediate Metabolizer" (IM).

The genotypic information was then used to predict the enzyme activity of CYP2C19 on mephenytoin (the marker used to measure the enzyme activity of CYP2C19). The global activity for each individual was determined by the combination of the activity corresponding to the proteins coded for each one of the two alleles, the result being the following phenotypes:

Phenotype extensive metabolizers (EM), normal activity: it indicates functional metabolic activity. The phenotypes are predicted from the combination of two active alleles.

Phenotype IM, intermediate activity: it indicates decreased metabolic activity. The phenotypes are predicted from the combination of an active allele and another allele without activity: */2 or */3

Phenotype PM, reduced activity: it indicates very decreased or absent metabolic activity. The phenotypes are predicted by the presence of two inactive alleles: 2/2, 2/3 or 3/3.

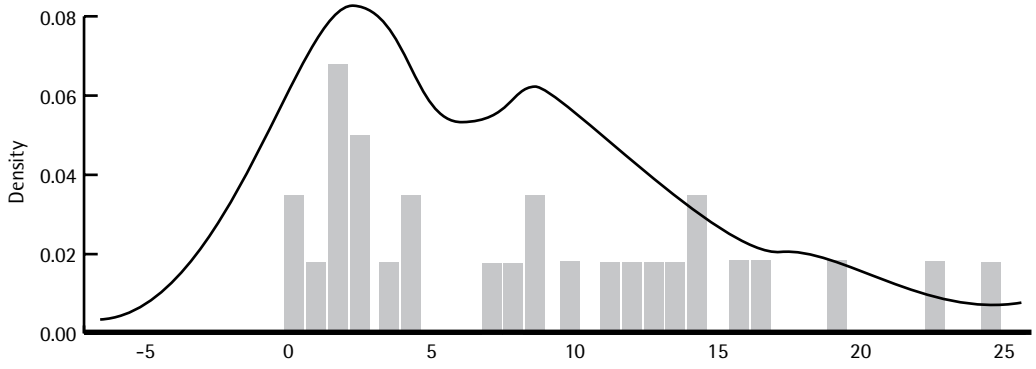

Figure 2 | *Curve obtained using the Gaussian Kernet Test on the post-DST Cortisol values. n the X axis, the values of cortisol obtain and on the 22. axis the density associated to each one of the values*

Table 1 Results of the PHARMACHIP® test, where N, I and R and its corresponding genotypes I/I, D/I and D/D indicate that the activity of the Serotonin transporter is Normal, Intermediate or Reduced, respectively while EM, IM and PM indicate that the metabolic capacity of CYP2c19 is Normal, Intermediate or very reduced, respectively

Serotonin Transporter SLC64A Deletion (D) or Insertion (I) of 44pb						CYP2C19 Determination of alleles 1,2,3 and 17				
Genotype %			Phenotype %			Genotype %		Phenotype %		
I/I	D/I	D/D	N	I	R	1/1	1/2	EM	IM	PM
43	43	14				69	31			
			43	43	14			69	31	0

RESULTS

The mean value of plasma cortisol obtained in the total sample was 6.5±5.6 mcg/dL. Analyzing the sample data using the Kernel Test, Figure 2, two principal population are distinguished, with a statistically significant difference between their means (Student T p<0.001). The first (n= 13, 45%, CORT Mean=9.0±2.1 mcg/dL, range: 5.4-12.9), corresponds to pharmacologically responder patients and with EM phenotype. The second population (n=10, 35%, CORT Mean=1.12±0.51 mcg/dL) groups the patients with PM phenotype, as a consequence of the combination of 1 or 2 alleles 2 and/or 3 of the CYP2C19 (genotype */2 present in 31% of the sample, in accordance with the data from the PHARMAchip® test, Table 1) together with belonging to one of the following groups: being a patient under treatment with potent inhibitors of said cytochrome (Omeprazole in 10 % of the patients), being a patients with age over 80 years (17%) or being under concomitant treatment with a second SSRI (Mirtazapine in 14 % of the sample). CORT values were superior to 13 in three patients (10%), this corresponding to patients who were non-responders to the doses used. Three others (10%) had intermediate values of CORT between 1.9 and 3.5, corresponding to IM phenotypes, as a consequence of belonging to one of the following groups: being a patient older than 70 years, being under concomitant treatment in moderate inhibitors of CYP 2C19 or having a single allele 2 or 3 in their genotype.

The range of values of post-DTS plasma cortisol values associated to each phenotypic group was: phenotype IM=1.2-3.5 mcg/dL, phenotype PM=0.6-1.7 mcg/dL and for phenotype EM=4.8-13.2 mcg/dL.

Finally, to calculate the equi-effective doses (dose that produces the same pharmacological effect, corresponding in our case to a post-DST plasma cortisol value equal to 10 mcg/dL) and the subsequent adjustment and calculation of nosologic regimes of Escitalopram, in accordance with the DST data obtained, we have proposed using the expression shown in Figure 3.

The application of the same range of sample values of CORT has allowed us to calculate the different nosologic regimes of the treatment with escitalopram for the different phenotypes present in the sample, which would be the following:

- Phenotype EM, Normality, (dose adjustment is not needed): Post-DST CORT values between 4.8 and 13.2 (mean±2 SD), range of dose of escitalopram between 10.4 and 31.0 mg.
- Phenotype IM, characterized by the presence of genotype */2 or */3 or concomitant treatment with moderate inhibitors of CYP2C19 or elderly over 70 years: post-DST CORT between 1.2 and 3.5, range of dose between 5.1 and 8.4 mg.
- Phenotype PM, characterized by the presence of genotype 2/2, 2/3 or 3/3, or the combination of genotype */2 or */3 with potent inhibitor drugs of CYP2C19 or with patients over 80 years or under treatment with a second SSRI, post-DST CORT values between 0.3-0.6, dose range: 3 to 4 mg.
- Non-responders and/or infra-dosed: post-DST CORT >14, doses superior to 30 mg.

$$\frac{[\Delta Cort]_1}{[\Delta Cort]_2} = 2^{\frac{[ISRS]_1}{[ISRS]_2} - 1}$$

Figure 3 *Expression of the calculation of the dose of Escitalopram and SSRI: [SSRI] 2 is the escitalopram(SSRI dose that associated to a post-DST cortisol value equal to 10, [SSRI]1 is the target dose, [ΔCort]2 is 10 mcg/dL and [ΔCort]1 is the plasma cortisol sought in the DST test*

For the different phenotypes, the following indexes for the equi-effective doses were obtained:

- Escitalopram dose (EM) / Escitalopram dose (PM)=4
- Escitalopram dose (EM) / Escitalopram dose (IM)=2

DISCUSSION

In the Therapeutic Drug Monitoring (TDM), the pharmacokinetics/pharmacodynamics models and/or genetic drug model (PK/PD and PK/PG) are used to search for the optimum theoretical therapeutic dose and to establish an adequate posologic scheme, being of capital importance the parameter with which the pharmacological action is evaluated, this being, normally, an easily measurable one.

In the present study, we have used a mechanistic PK-PD model. This model was used on the already verified fact that patients with depression have augmented activity of the HPA axis and altered regulation by negative feedback. Escitalopram produces an up-regulation of the dose-dependent CRH receptors, which may be measured using the DST test. Once the steady-state is achieved, it serves for the dosing of Escitalopram and other SSRIs, using the expression in Figure 3 for dose adjustment.

The reduction of the activity of the HPA axis (reduction of baseline value of CORT) after 4 weeks of treatment with escitalopram is associated with the reduction of the depressive symptoms, this being the best predictor of the antidepressant efficacy. Thus, the DST test in depressed patients seems to be a potential biomarker for the serotonin selective reuptake inhibitors (SSRI), the hyperactivity of the HPA axis becoming normal in depressed patients if treated with SSRI for several weeks through the regulation of the mineralocorticoid and glucocorticoid receptors and the decrease of the expression of CRH, with improvement of the function of the receptor of the mineralocorticoids and the restoration of the control of the altered feedback.

In regards to the PK/PG model, the genotypic sample data obtained, Table 1, indicate that the alleles 2 and 3 of the del CYP2C19 and their combinations lead to PM and IM phenotypes, with an equi-effective dose ratio for the different EM/IM phenotypes=2 and EM/PM=4, the interactions being drug-drug, whether pharmacodynamics (Mirtazapine and SSRIs) or pharmacokinetics (Omeprazole and ibuprofen [IBPs]), a safety problem because multiple drug treatment is a common clinical practice in Psychiatry. The risk of overdosage of escitalopram when taken in combination with IBPs and Omeprazole specifically (the IBP being of more extended use in Spain) is very high due to the potent inhibition of CYP2C19 it provokes after approximately 7 days of combined treatment with Escitalopram.

The use of the PK-PD and PK-PG models in the therapeutic monitoring of Escitalopram is justified because of the pharmacological behavior of the SSRIs that is inferred from the study of its Antidepressive Dose-Response curves:

The Antidepressive Dose-Response Curve presented by the SSRIs has a flat form or platue form, this meaning that the maximum clinical response may be achieved with low drug doses. The minimum effective dose of escitalopram has not been convincingly established as of yet. However, a meta-analysis of placebo-controlled studies concluded that 10 mg / day of Escitalopram is the dose that is generally effective in patients who do not suffer severe major depression and 20 mg /day is the minimum dose of Escitalopram in the rest of the cases. These doses allow for an inhibition of approximately 70 to 80% of the serotonin reuptake.

We have found that each one of the 3 different phenotypes identified (PM, IM and EM) would correspond to a different minimum effective dose, this being, approximately and respectively, 3-4, 5-8 and 10-30 mg/day and that these are a consequence of the different possible combinations between the individual genotype and the presence or not of interactions with potent inhibitors of CYP2C19 such as the IBPs (pharmacokinetics), the association with other SSRIs (pharmacodynamic interaction) and the age of the patient that conditions the amount of CYP2C19 enzyme present in the body, without overlooking many others of less importance.

The flattened form of the antidepressive dose-response curve suggests that "on the average" no patient would benefit from a different dose than that normally effective. However, since the antidepressant effect and the adverse effects of the SSRIs are dependent on the plasma levels of the drug and since the plasma levels and given that the same dose differs between one patient and another, some patients will need different doses (higher or lower, according to the case) to achieve the same levels. Clinical evaluation of the response can be used to detect these patients. However, to do so, it would be necessary to be able to distinguish between the dose-dependent adverse effects that imitate the symptoms of depression and the true depressive symptoms. Thus, it is important to apply the TDM using the DST test in order to obtain the CORT value, a biomarker of the plasma level or biophase of Escitalopram, in the first stages of the treatment. This would allow us to make a prompt adjustment of the dose and thus avoid severe toxicity, principally in patients with deficiency of CYP 2C19, independently of it having a genetic origin or being due to potent inhibitor drugs of the CYP that are administered jointly with escitalopram, and to increase efficacy and tolerance, adjusting the drug upwards in the patients who have a rapid clearance and downwards in those with slow clearance.

The latter reason would be applicable to drugs such as the SSRIs, which have a sufficiently wide therapeutic index

so that the severe toxicity would not be of concern, but which, however, can cause a greater increase of the adverse effects that may be confused with the lack or loss of efficacy.

The TDM of escitalopram and other SSRIs provides an aid to the clinician in the decision-making process, informing the clinician about the greater or lesser sensitivity of a certain patient to a dose of escitalopram, about the plasma concentration reached and the possibility of lack of total or partial adherence to the treatment prescribed. The final purpose of the therapeutic drug monitoring (TDM) would therefore be to assure that each patient would receive the necessary dose to reach the therapeutic levels of the drug, together with other considerations such as clinical course and tolerance.[21]

Finally, and in regards to the limitations of the present work, it should be mentioned that the most important one is that of the small sample size. This limitation does not take validity away from the data, it being possible for us to quantify globally but not individually the influence of each one of the principal variables that affect the posological regime of Escitalopram and hinders the identification of the multiple secondary variables.

CONCLUSIONS

It has been verified that the Dexamethasone Suppression test can be used as a biomarker of the pharmacological response to escitalopram and as an instrument for the calculation of the posological regimes corresponding to the three phenotypes present.

The use of said test provides significant data on the different phenotypes of Escitalopram when this is metabolized by CYP2C19 (PM, IM and EM) and the presence or not, as well as the intensity, of the pharmacokinetic interactions with other drugs that affect said cytochrome and of the pharmacodynamic interactions with the other with which Escitalopram shares the action mechanism.

Finally, an expression for the calculation of the nosological adjustment of Escitalopram has been proposed, based on the data of cortisolemia obtained in the DST test.

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