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Biomarkers and Therapeutic Drug Monitoring in Psychiatry

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1. Introduction

The World Health Organization, WHO, reported in 2010 that there were approximately 490 million (7%) of people suffering from mental disorders, such as abuse of alcohol and other substances, major depression, bipolar disorder, schizophrenia and dementia, recommending research the pathophysiology of these disorders in order to improve their understanding and to develop more efficient and cost-effective interventions (WHO 2001, 2005).

The diagnosis of mental disorders, should be based on objectively measurable parameters and, also, should help us to establish therapeutic guidelines, based on the etiology of the diseases, and their adaptation to each individual. The absence of an objective biological test for the diagnosis of mental disorders which would constitute the Gold Standard for this task, along with the frequent psychiatric comorbidity, heterogeneity and, polygenic and multifactorial etiology, requires the search for Biomarkers that facilitated the diagnosis and treatment of the psychiatric illnesses. The Convergent Functional Genomics has revealed that proteins, compounds of biochemical nature related to different physiological functions, genetic tests for diagnosis or, even, different functional tests such as, for example, the dexamethasone suppression test, DEX, used to study the function of the hypothalamic-pituitary-adrenal axis, HPA, can be candidates (Avissar & Schreiber 2003; Kemperman 2007; Russell 2004).

The use of Biomarkers, that is, a physical characteristic, or a biochemical or biological parameter, objectively measurable and quantifiable, that report the evolution and condition of certain normal physiological processes or pathological, or response to a therapeutic intervention, pharmacological or otherwise, is relatively new but this field has gained much interest in recent decades among clinicians and researchers. A Biomarker, as a measurable biological entity that points the presence or absence of a disease, a toxin, a biological condition, a genetic pattern, or a therapeutic response to a drug, must be related quantitatively with the disease progression and/or therapy (http://www.gaba-network.org; Biomarkers Definitions Working Group, BDWG, 2001).

Biomarkers, are utilized in psychiatry not only as tools that aid us in the diagnosis and treatment of various diseases, facilitating the use of therapies aimed at specific groups or individuals, but also, as Surrogate Markers or Clinical Surrogate Endpoints for PK, PD and

PG modelling in drug response, and to investigate the biological mechanisms of action and the efficacy and safety profile of the target drug, being this last point developed along this chapter (Riggs 1990).

The search of a Biomarker begins with the selection of the groups of patients and controls, continous with the selection of the type of sample to use and, finally, the selection of the statistical analysis that allowed us to demonstrate differences between both groups, such as the multivariate analysis of cross-sectional data and multivariate correlation analysis of longitudinal data, so that, there was clear evidence that these Biomarkers are able to distinguish between controls and affected individuals. To complete the validation, we have to check this on a large group of patients following Food and Drugs Administration guidelines (FDA 2008). In the case of Biomarkers used to monitor pharmacological therapies, the choice and validation of these should be supported, in addition, on studies of the etiology of the disease being treated and mechanism of drug action, as well as provide data on its cost-effectiveness and its side effects (Kemperman 2007).

In the other hand, a Surrogate Marker, defined as a laboratory measurement, physical sign or symptom, is used in therapy as a direct measure of how patient feels, functions, or survives and is expected was able to predict the effect of a treatment, ie, it is a test that is used as measure of the effect of a given specific treatment. It is a candidate Biomarker if it can be validated, taking this atribute when the evidence has proven that the predicted effect induced by drugs or other therapy, on the Surrogate Marker, produces the outcomes desired on the clinical characteristic of interest, such as blood pressure, serum cholesterol, intraocular pressure, etc, while Clinical Surrogate Endpoint refers to the final desirable value that we want to achieve for a specific Surrogate Marker, which is related to the level of disease progression, intensity of a symptom or sign, or a laboratory test, that constitute the desired target and that reflect the expected clinical outcome (BDWG 2001).

To validate a Surrogate Marker as a Biomarker, we need to understand the biological relationship between the Surrogate Marker that predicts the desired clinical benefit and the clinical outcome achieved. For pharmacological treatments, we have to know, moreover, all therapeutic actions, if we want to conclude that the effect obtained on the Surrogate Marker will result in the beneficial clinical outcomes desired. (Buckley & Schatzberg 2009; Russell 2004).

In short, at the present time the biological causality of most psychiatric illnesses and the intimate mechanism of action of most psychotropic drugs are unknown. However, it is possible to modulate pharmacologically a large number of neuroreceptors, using this tool as target of drug therapies and utilizing to control of psychiatric disorders symptoms. We will review in this chapter, the role and potential use of Biomarkers and / or Surrogate Markers to optimize the pharmacological treatments of most common psychiatric illnesses, with emphasis on schizophrenia and depression, in order to use them in the dosage regimen calcualtion and choosing a particular therapeutic drug strategy (Noll 2006; Shaheen 2010).

2. Models for therapeutic drug monitoring

After the administration of a drug, several processes occur leading to the pharmacological effect, so that we can define Pharmacokinetics, PK, as "what the body does to a drug" and pharmacodynamics, PD, as " what the drug does to the body " (Geldof 2007).

There are three unitary models for the therapeutic drug monitoring:

1. Pharmacokinetic models, PK. They are used to describe control processes of drug concentration in biological fluids at any time after its administration, being absorption, distribution, metabolism and excretion, the main stages that determine the evolution of the drug concentration versus time, so the PK-models, determine the overall course of the process (Perez-Urizar 2000).
2. Pharmacodynamic models, PD. They are used to describe the relationship between the drug concentration and/or active metabolites and the magnitude of the pharmacological effect obtained such as, eg, blood pressure, heart rate, etc (Geldof 2007; Holford & Sheiner 1981; Rowland & Tozer 1995; Sheiner et al 1997) .
3. Pharmacogenetic models, PG. They are used to describe the influence of interindividual genetic variations in the response to a drug in terms of efficacy and safety. They use genotype-phenotype, gene-concentration and gene-dose correlations for predicting the phenotype of a individual and provide support to achieve a optimal pharmacotherapy.

As important part of the construction of these models, a Surrogate Marker or Biomarker is defined as measure that characterizes, in a strictly quantitative manner, the various processes and stages that occur between the administration of a drug and its pharmacological effect, and can be used in clinical practice for the individualization of drug therapy, from the viewpoint of dosage regimen calculation and therapeutic strategy. In fact, there is a growing interest in the use of biomarkers in drug development, as is reflected in the publication of numerous reviews and comments, appeared recently, on this topic. As well as, the recent increase in the number of publications about PK-PD models in journals of Clinical Pharmacology and Clinical Pharmacy, concerning to theoretical models and their implementation. Despite the continued increase in the number of articles, there are still, a large number of publications that contain pharmacokinetic and pharmacodynamic data without PK-PD modeling studies (Francheteau 1993; Geldof 2007; Mandem & Wada 1995; Zuideveld 2001).

Optimization of pharmacologic treatment is usually done by monitoring serum drug concentrations, in PK models, or by the direct or indirect pharmacological response, represented by Biomarkers or Surrogate Markers, in PD models, combined with pharmacogenetic and environmental characteristics, in PG models.

PK models can be non-parametric or compartimental. Non-parametric models provide an empirical description of the temporal evolution of drug concentration in terms of the maximum concentration, Cmax, and time needed to reach it, Tmax, and area under the concentration versus time curve, AUC. While compartmental models provide a description of concentration profile versus time of the drug in a body fluid compartment (Csajka & Vérotte 2006; Geldof 2007; Holford & Sheiner 1982; Perez-Urizar et al 2000).

Binary models PK-PD, PK-PG and PD-PG, as a result of the union of simple models, are aimed to find out the suitable therapeutic dose, body "clearance" and other kinetic parameters related to plasma drug concentration or pharmacological effect, establish an adequate dosage scheme to achieve the desired therapeutic goal, as well as know the time evolution of the pharmacological effect, using the appropiate model and the individual genotype of the different populations to which treatment is targeted, by using the following mathematical tools:

1. General equation of the dose-response relationship, receptor mediated, which relates the intensity of the pharmacological effect, E, with the concentration of the drug, D, and of the receptor, R, presents in the body:

$$\frac{\partial^2 E}{\partial D^2} = \left(\frac{dD}{dR}\right)^2 \frac{\partial^2 E}{\partial R^2} \quad \text{Where} \quad \frac{dD}{dR} = K(cons\tan t) \tag{1}$$

Once the steady-state and a pharmacological response, ranging between the 20-80% of maximal effect, is reached we can estimate the optimal dose required to achieve the desired Clinical Surrogate Endpoint, using the following expression, an approximation of the equation 1:

$$\frac{[\Delta CSE]_1}{[\Delta CSE]_2} = 2^{\left[\frac{(DD)_1}{(DD)_2}\right]-1} \tag{2}$$

Where $[\Delta CSE]_1$ is the Clinical Surrogate Endpoint of the drug, equivalent to the average increase (delta, Δ) value obtained for CSE in the patients drug treated, $[\Delta\ CSE]_2$ is the experimental delta value obtained for CSE in a individual, $(DD)_2$ is the dose of drug with which has been obtained a $[\Delta\ CSE]_2$ value equal to 10 and $(DD)_1$ is the drug target dose (Lozano et al 2007,2008a,2008b, 2009b,2010a,2010b,2010c, 2011a).

2. Hill`s equation, equation 3, a partial solution of the above equation 1, from which comes, which relates the intensity of the pharmacological effect, E, on the Biomarker with the concentration of drug in the body, C, (Hill 1910):

$$E = \frac{C^{\gamma} E_{\max}}{C^{\gamma} + EC_{50}^{\gamma}} \tag{3}$$

3. Kernel density estimation, Kernel`s test, used for poblational analysis, performed in the PK-PG and PD-PG models, which incorporate pharmacogenetic analysis (Wessa 2008).
4. Finally, for interaction-based models, where two or more drugs that interact on the same receptor, the following equation, equation 4, serves to describe the relation between the reaction velocity, $d_V/d_{C,}$ of a drug, A, with the receptor, , versus to that of another drug, B, on the same receptor:

$$\frac{d_{Va}}{d_{Ca}} = -\frac{d_{Vb}}{d_{Cb}} \tag{4}$$

(Lozano et al 2009a, 2009c, 2010d).

2.1 PK-PD models

Consist of mathematical expressions that describe the quantitative relationships between the response intensity of a Biomarker or Surrogate Marker and drug dose applied. They have three components: a PK model, which characterizes the temporal evolution of the concentration of the drug and/or active metabolites, in blood or plasma, a PD model that characterizes the relationship between a drug concentration and/or possible active

metabolites to the pharmacological effect, and finally, an aggregate model that takes into consideration other factors that may affect the pharmacological effect, frequently observed in the models of compartmentalized pharmacological effect and in those of indirect pharmacological response (Breimer & Danhof 1997; Geldof 2007).

The PK-PD models, can be:

1. Mechanistic-based models, which characterize the time course of drug effect, "in vivo", using expressions that describe the biophase drug distribution, target-drug binding, target-drug activation and feedback homeostatic processes and contain elements corresponding to the distribution in the target site , target-drug binding, and activation and transduction. They are based on the principles of receptor theory, that characterizes the interaction of the receptor with the drug in terms of affinity and intrinsic activity. In these models, PK-PD, when steady-state is reached, drug concentration in the biophase is paralell to the plasma concentration and directly proportional to the dose (BDWG 2001; Geldof 2007; Sheiner et al 1979 Van der Graaf & Danhof 1997).

Under stable conditions, relatively simple models, such as those linear or log-linear, can be used to characterize the dose-response relationship. The most used is the sigmoid model, which is an empirical function to describe the nonlinear relationship between drug concentration and the pharmacological effect; this model is mathematically expressed by the general equation for dose-response curve, equation 1, or also by Hill`s equation, equation 3, a partial solution of the previous, where E is the pharmacological effect observed with a given dose , E_0 is the response in the absence of drug, E_{max} is the maximum effect or intrinsic activity of drug, C is the concentration of drug and/or metabolite in plasma and/or biophase, EC_{50} is the concentration of drug and / or metabolites that produce 50% of maximal effect, potency, and γ is the Hill factor, that expresses the sigmoidicity of the curve (Geldof 2007; Hill 1910; Holford & Sheiner 1982; Meibohm & Derendorf, 1997).

Under conditions of non steady-state , the basic models PK-PD are unable to describe the time evolution of the pharmacological effect. Factors such as the compartimiental effect, acute tolerance and sensitization, and indirect response modeling, can explain the dissociation, frequently observed, between the temporal evolution of the drug concentration and pharmacological effect, using, in these cases, the previous model but applied to different doses to simulate the change in concentration along the time (Bauer et al 1997; Dayneko et al 1993; Derendorf & Meibohm 1999; Jusko & Ko 1994; Ragueneau et al 1998; Sheiner et al 1979).

2. Indirect response models, are based on a combination of the inhibitor or stimulant effect, that can produce the drug, and the factors controling the increase or decrease of the pharmacological response, represented by the constants K_{in} and K_{out} (Derendorf & Meibohm 1999, Mager et al 2003; Meibohm & Derendorf 1997; Rowland & Tozer 1995).
3. Drug interaction-based models, are used to describe the influence of two or more drugs among them, acting on the same receptor. Their use are limited to situations in which several drugs are administered together, or when a drug becomes an active metabolite. In theoretical terms refer to the prediction of the combined effects of more than one drug. The general approach to the study of these interactions involves the analysis of changes in the velocity of reaction that occur when the drugs are used combined or separately (Lozano et al 2009a, 2009c, 2010d).

4. Poblational models, are used to solve the problem of inter and intra-individual variability in the therapeutic response to a drug. In PK and PD models, the kinetic parameters of each individual are modeled in terms of the fixed effect observed, and other of random nature, while PK-PD poblational models, based on nonlinear mixed effects analysis, characterize the pharmacokinetic parameters and concentration-effect relationship, in poblational terms more than individual. Thus, in PK and PK-PD poblational models, we need to know in advance the average behaviour of pharmacokinetic parameters in target population, to identify and assess demographic, pathophysiological and environmental factors, affecting population under study and, finally, evaluate the inter and intraindivual variability through the variation coefficient of the PK parameters and their residual components (Dominguez-Gil & Lanao 1999; Schnider et al 1996).

2.2 The PK-PG models

Consist of mathematical expressions that describe the quantitative relationship between the drug dose necessary to achieve the same response intensity of a Biomarker or Surrogate Marker, for each one of the different genotypes phenotypically actives present in a population.

Pharmacogenetic models, PK-PG, are used to adapt the therapeutic use of different drugs to the idiosyncrasy of each patient and their genetic characteristics, increasing its efficiency and minimizing their side effects. Approximately 20-90% of the interindividual variability in drug response is consequence of individual genotype and variants that encode different polymorphs of the enzymes that metabolize and / or transport drugs.

Single Nucleotide Polymorphisms, SNPs, have been associated with substantial changes in the metabolism or in the effect of a drug, and therefore are being used to predict the clinical response to a drug of an individual. For the biotransformation of a drug, there are over 30 families of metabolizers enzymes belonging the family of cytochrome P-450, whose genetic polymorphisms normally lead to a functional changes in the encoded protein, resulting in individuals with different phenotypes:

a. Poor Metabolizers, PM: The encoded enzyme has no activity, the metabolic activity is very reduced or absent and the phenotype is predicted by the presence of two inactive alleles.
b. Intermediate Metabolizers, IM: The encoded enzyme has its activity decreased, the phenotype is predicted by the presence of two alleles with decreased activity, or a combination of a reduced activity allele and a allele with no activity.
c. Extended metabolizers, EM: They are carriers of one active gene copy at least, have a normal metabolic activity and phenotype is predicted from the combination of two active alleles. For some genes, the presence of one active allele combined with one allele with decreased activity or allele with no activity, causes that the metabolic activity was normal.
d. Ultrafast Metabolizers, UM: They have a double metabolic capacity and the phenotype is predicted by the presence of three or more functional alleles or the presence of two inducible alleles http://cpmc.coriell.org/Sections/Medical/DrugsAndGenes_mp.aspx?PgId=216).

Carrier proteins of drugs play an important role in regulating the absorption, distribution and excretion of many drugs. Within the ATP-binding cassette family, P-glycoprotein,

encoded by the ABCB1 gene, is one of the best known , being its main function the control of the outflow from inside the cells of certain endogenous and / or exogenous substrates, including several drugs and substances such as bilirubin, so the presence of polymorphisms in this gene, entails changes in the PK and PD of certain drugs.

2.3 The PD-PG models

PD-PG models, consist of mathematical expressions that describe the quantitative relationship between the response intensity of a Biomarker or Surrogate Marker, to a single dose of the drug, and the different genotypes phenotypically actives present in a specific population.

Pharmacogenetic models, PD-PG, are used to adapt the therapeutic use of different drugs to the idiosyncrasy of each patient and their genetic characteristics, increasing its efficiency and minimizing their side effects. Approximately 20-90% of the interindividual variability in drug response is consequence of individual genotype and variants that encode different polymorphs of therapeutic targets.

Genetic polymorphisms with indirect effects on the response to drugs are those that affect to a genes encoding proteins that often are involved in the mechanisms of the drug disposition, producing alterations in the response to treatment only under certain situations.

Therefore, both PK -PG and PD-PG models are used to describe the genotype-phenotype, gene-concentration and gene-dose correlations, necessary to achieve an optimal pharmacotherapy (Brockmöller & Tzvetkov 2008, Tsai & Hoyme 2002; Weinshilboum & Wang 2006).

3. Biomarkers for therapeutic drug monitoring in psychiatry

3.1 Lithium

Bipolar disorder, BD, is characterized by the presence of one or more episodes of mania or, in mild cases, hypomania and additional depressive episodes, concomitants or alternants.

The cause is unknown, although recent studies suggest the presence of an imbalance between excitatory neurotransmitters, mainly glutamate, and inhibitors, principally GABA, as well as alterations in cation pumps, such as of sodium and of calcium, which would explain the pathogenesis of bipolar disorder and another pathologies as epilepsy (Brown & Sherwood 2006).

To explain the action mechanism of Lithium salts there are several proposals, being the most known:

1. Inhibition of the enzyme GSK-3B, whose complete mechanism in relation with BD has not yet been hypothesized (Jonker et al 2003).
2. Blockade of the NMDA/ NO receptor: The Nitric Oxide, NO, plays a crucial role in neuronal plasticity, having shown that the NO system may be involved in the antidepressant effect of lithium amd the increase in antidepressant capacity of lithium by the blockade of NMDA receptor would indicate an involvement of the NMDA/NO receptor in the pharmacological action of lithium (Ghasemi et al. 2008, 2009a, 2009b; Ghasemi & Race 2008).
3. Inhibition of Inositol monophosphatase enzyme (Einat et al 1998).

All the pharmacological activity of lithium salts is carried out by the insolubilization of intracellular inorganic phosphate salts through the formation of inorganic lithium phosphates. These ones have much lower solubility than their sodium salts (eg the solubility of Li_3PO_4 in water is 0.03821 g/dL/20 ° C versus of the Na_3PO_4 that is 8.8 g/dL/25 ° C), which leads to decrease the amount of intracellular inorganic soluble phosphates, P_i, causing, consequently, decrease in intracellular phosphate stored in organic compounds, P_o, and slowdown all metabolic reactions that involve exchange of inorganic phosphates, mainly those using ATP but, also, those using another nucleotides with capacity for the storage of phosphates, as we know now , and affecting in a hierarchically manner to several intracellular pathways of activation and/or inhibition, being those of GSK and inositol-phosphates, among other, the first to be affected (Lozano et al 2009a, 2010a,2010b).

In the case of the thyroid gland, lithium salts cause a dose-dependent decrease in serum free thyroxine, FT_4, due to the very low solubility of inorganic lithium phosphates, formed in the interior of target cells by action of lithium, which leads to a decrease in the intracellular pH and in the tyrosine iodination reaction, pH dependent, with consequent decrease of the FT_4 levels, because the iodination of phenols is a direct reaction of iodine, I_2, on the phenolate ion, very sensitive to changes in pH, decreasing exponentially the rate of iodination when the pH does it (Kessler et al 2008; Lozano et al 2010a, 2010b; Taylor & Evans 1953).

3.1.1 PK-PD model

Mechanistic-model. We can use the FT_4 levels in plasma as a biomarker for quantifying the intraneuronal concentration of Lithium and the dosage regimen calculation in the treatments of bipolar disorder with salts Lithium, increasing o decreasing the daily dosage to reach FT_4 values, in the range of 1.02-1.08 ng/dL, its Clinical Surrogate Endpoint (Lozano et al 2010a, 2010b).

3.1.2 PK-PG model

Due to the Lithium elimination by glomerular filtration, the poblational analisys conducted by Kernel`s test has allowed us to detect two subpopulations related to serum creatinine and therefore with the Lithium Clearance, caused by the presence of MDR1 polymorphisms, altering the aldosterone level and therefore the Creatinine Clearance, obtaining from the application of the equation 2, the following equi-effective dose ratio:

$$\frac{\text{DOSE}\ (\text{genotype:wild type})}{\text{DOSE}\ (\text{genotype:polimorphic type})} = 1.5 - 2$$

(Lozano et al 2011b).

3.1.3 PK-PG model

Poblational analysis conducted by Kernel`s test has not detected any subpopulation.

3.2 Escitalopram-SSRI

Depression is a pathological alteration of mood, being Major Depressive disorder the most studied with a prevalence of 10-25%. Its complex origin, is attributed to a defective

transmission of noradrenaline and dopamine associated with dysregulation of the hypothalamic-pituitary-adrenal axis , HPA, which is reflected by the alteration of the cortisol escape from suppression by dexamethasone in the Dexamethasone Suppression test, DEX test, and by the increased response of cortisol in the Dexamethasone-Suppressed Corticotropin-Releasing Hormone Stimulation Test, DEX-CRH test. The decrease in serotonergic transmission in the brain and increased secretion of cortisol in patients with major depression have reached the status of an axiom in textbooks, being the cortisol the biological key mediator through which the brain slows down serotonergic transmission that causes depression in vulnerable people (American Psychiatric Association 2000; Dinan, 1996; Goodwin & Post 1983; Noll 2006; Schnider et al 1996).

Deregulation of the hypothalamic-pituitary-adrenal axis is present in a high rate among the patients with depression and its normalization, observed by the response to the DEX-CRH test, is verified when there is a good response to pharmacological treatment. Moreover, the serotonergic system interacts with the hypothalamic-pituitary-adrenal axis and, because of this, the stimulation of this axis can be used as a Surrogate Marker for the pharmacological action of the 5-HT agonist in the CNS (Cowen 1993, 1998; Gartside & Cowen 1990; Meltzer & Maes 1994; Meltzer et al 1991).

The reduced serotonergic neurotransmission is well known feature of the depression and therefore it is not surprising that SSRI drugs were the first line of treatment in depressive disorders. Plasma levels of Escitalopram and another SSRI drugs decrease the HPA-response in the DEX test and there is a good correlation between dose of the SSRI drug and decreasing of plasma cortisol. Cortisol values obtained by Nugent's test, can be used as a Biomarker or Surrogate Marker for dosage regimen calculation of antidepressant drugs that act on serotonergic regulation of the HPA axis. The SSRI drugs whose main action is the activation of serotonergic transmission, produce a decrease of plasma cortisol value obtained by Nugent`s test, in dose-dependent manner and can be used as surrogate marker of SERT-carrier occupation and 5-HT receptor activation by the Escitalopram and/or other SSRI drugs and to serve for their dosage regimen calculation (Bel & Artigas 1992; Berkenbosch et al 1987; Bosker et al 1994; Hsieh et al 2010; Ising et al 2005, 2007; Knorr et al 2011; Maes et al 1993; Meltzer 1985; Nordstrom & Farde 1998; Sasayama et al 2011; Schule et al 2009).

3.2.1 PK-PD model

PK-PD mechanistic-model. Around 50-60% of patients with depression have an increased activity of the hypothalamic-pituitary-adrenal axis and altered its regulation by negative feedback. Escitalopram and other SSRI produce an up-regulation of CRH receptors in a dose-dependent manner that can be measured by Nuggent`s test and this can be used for dosage regimen calculation of escitalopram and other SSRIs.

Once the steady-state and a pharmacological response, ranging between the 20-80% of maximal effect, is reached we can estimate the optimal dose required to achieve cortisol values of 9.0 ± 2.1 mcg/dl, its Clinical Surrogate Endpoint, using equation 2 (Lozano et al 2008a, 2011a).

3.2.2 PK-PG model

Metabolic studies for Escitalopram /Citalopram indicate that CYP3A4 and CYP2C19 are the major isozymes involved in N-demethylation of Escitalopram /Citalopram. The alleles

CYP2C19 * 2, CYP2C19 * 3 and CYP2C19 * 17 CYP2C19 and their combinations lead to phenotypes PM and IM, obtaining from the application of the equation 2, the following equi-effective dose ratios:

$$\frac{\text{DOSE}\left(\text{CYP2C19 phenotype}:\text{EM}\right)}{\text{DOSE}\left(\text{CYP2C19 phenotype}:\text{IM}\right)}=2 \text{ and } \frac{\text{DOSE}\left(\text{CYP2C19 phenotype}:\text{EM}\right)}{\text{DOSE}\left(\text{CYP2C19 phenotype}:\text{PM}\right)}=4$$

Paroxetine, Fluoxetine and Sertraline, which are metabolized by the CYP2D6 whose activity ranges considerably within a population and includes Ultrafast metabolizers, UM, Extensive metabolizers, EM, Intermediate metabolizers,IM, and Poor metabolizers, PM. Among these are fully functional alleles, alleles with reduced function and null, non-functional, alleles, which convey a wide range of enzyme activity, from no activity to ultrarapid metabolism of substrates. Null alleles of CYP2D6 do not encode a functional protein and have no detectable residual enzymatic activity, being responsibles for the PM phenotype in homozygous and for IM phenotype in heterozygous, when to present (Zhou 2008), obtaining from the application of the equation 2, the following equi-effective dose ratios:

$$\frac{\text{DOSE}\left(\text{CYP2D6 phenotype}:\text{EM}\right)}{\text{DOSE}\left(\text{CYP2D6 phenotype}:\text{IM}\right)}=2 \text{ and } \frac{\text{DOSE}\left(\text{CYP2D6 phenotype}:\text{EM}\right)}{\text{DOSE}\left(\text{CYP2D6 phenotype}:\text{PM}\right)}=4$$

(Lozano et al 2008a).

3.3 Antipsychotics

Schizophrenia first described by Benedict Morel in 1853 and with a prevalence of 1% in the general population, represents a group of chronic and severe mental disorders. Although its origin is unknown, there is an increased dopaminergic activity in the mesolimbic pathway of the brain. This biochemical alteration is used as target for the drug treatment of this disease, being the blockade of dopamine D_2 receptors in the limbic system important for the control of the psychotic symptoms and the blockade of $5HT_{2a}$ receptor for the control of negative symptoms.

Despite the unknown action mechanism of antipsychotic drug, is known that all of them act on the dopaminergic system but their affinitiy for dopamin and serotonin receptors,D_2 and 5-HT, are different, being necessary the blockade of these receptors for its pharmacological action, being the combined blockade of the receptors 5-HT_{2a} and D_2 a method that evidence has proposed for the treatment of schizophrenia (Horacek et al 2006).

Prolactin plasma level, PRL, reflects the tuberoinfundibular D_2 blockade and can be used as a Biomarker or Surrogate Marker for drugs affecting dopaminergic system and, in general, for atypical antipsychotics which main action was the blockade of D_2 receptors, since they produce a dose-dependent prolactin increase that can be used as a surrogate for D_2 receptor occupation and to serve at the same time for the dose adjustment and/or, by extension, the absence of prolactin increase levels after antipsychotic treatment could be considered a surrogate of a decrease occupancy of the D_2 receptor, as for Aripiprazole. Eventually, low occupancy of D_2 receptors in the striatum can be used as Surrogate Marker for the likelyhood of motor side effects (Avrantis & Miller 1997; Kapur et al 2000; Meltzer 1985; Nordstrom & Farde 1998).

Prolactin plasma levels are also high in several drug treatments, such as: (a) Those that are expected to increase extracellular 5-HT levels in the brain as L-tryptophan, and 5-hydroxytrytophan, (b) those that acting stimulating different types of 5HT receptors, and some, but not all, $5HT_{1a}$ selective agonists. In all these cases, prolactin plasma level becomes a surrogate of the increase of serotonergic transmission in one or more regions of the brain. The blockade of this effect, by an antagonist drug of the 5-HT receptors, appropriate and specific, can serve, in turn, as a substitute for the ability of a drug for the functional antagonization of the receptor (Goddard 1993; Golden et al 1989; Murphy et al 1996;; Seibyl et al 1991; Seletti et al 1995; Silverstone & Cowen 1994).

3.3.1 Risperidone

Risperidone, an atypical antipsychotic with high affinity for dopamine receptors D_2 and Serotonin $5\text{-}HT_{2a}$, produces a dose-dependent D_2 receptor occupancy in the mesolimbic system, necessary for the control of the disease, while the blockade in the nigrostriatal would be responsible for extrapyramidal side effects and in the tuberoinfundibular of the hiperprolactinemy.

3.3.1.1 PK-PD model

Mechanistic-model. Risperidone produces a blockade of D_2 receptor in the tuberoinfundibular system causing a dose-dependent increase in prolactin that can be used for dosing it. Using the values of serum prolactin, obtained in the morning before administration of Risperidone and not before steady-state plasma levels , minimum concentration in "steady-state", are reached we can construct the dose-response curve of prolactin plasma level versus Risperidone dose, which fits a rectangular modified hyperbola, equation 5, and permit us to establish a maximum value of PRL= 80-90 (40-45) ng/ml and a minimum value of PRL= 40-50 (20-25) ng/ml, for the optimal dose of risperidone, in women and men, in parentheses (Lozano et al 2007, 2010c):

$$PRL = \frac{84 Risp^2}{90 + Risp^2} \tag{5}$$

3.3.1.2 PK-PG model

Risperidone is eliminated by metabolism mainly through the action of citochrome CYP2D6, and to a lesser extent through CYP3A4. Risperidone and its main metabolite, 9-OH-risperidone, constitute the "active fraction" with an elimination half-life of 6 and 24 hours, respectively, in extensive metabolisers, EM, and 20 and 30 h in the case of patients with phenotype "poor metabolizer" PM. The "clearance", Cl, for the active fraction of Risperidone is respectively of 5.0 and 13.7 l/h in EM subjects and 3.2 and 3.3 l/h in individuals PM (Janssen Research Foundation 1994).

The CYP2D6 activity ranges considerably within a population and includes Ultrafast metabolizers, UM, Extensive metabolizers, EM, Intermediate metabolizers,IM, and Poor metabolizers, PM. Among these are fully functional alleles, alleles with reduced function and null, non-functional, alleles, which convey a wide range of enzyme activity, from no activity to ultrarapid metabolism of substrates. Null alleles of CYP2D6 do not encode a functional protein and have no detectable residual enzymatic activity, being responsibles for

the PM phenotype in homozygous and for IM phenotype in heterozygous, when to present (Zhou 2008), obtaining from the application of the equation 2, the following equi-effective dose ratios:

$$\frac{\text{DOSE}\left(\text{CYP2D6 phenotype}:\text{EM}\right)}{\text{DOSE}\left(\text{CYP2D6 phenotype}:\text{IM}\right)}=1.5 \quad \text{and} \quad \frac{\text{DOSE}\left(\text{CYP2D6 phenotype}:\text{EM}\right)}{\text{DOSE}\left(\text{CYP2D6 phenotype}:\text{PM}\right)}=3$$

(Lozano et al 2007, 2010c).

3.3.1.3 PD-PG model

The poblational analysis of PRL values, using Kernel`s test, allowed us to detect two subpopulations, sex-linked, and related to an alteration of the dopaminergic and / or serotonergic pathways, caused by a combination of polymorphisms of the genes encoding receptors 5-HT_{2a} , D_2, and SERT, among others, obtaining from the application of the equation 2, the following equi-effective dose ratio:

$$\frac{\text{DOSE}\left(\text{genotype}:\ \text{wild type}\right)}{\text{DOSE}\left(\text{genotype}:\ \text{polimorphic type}\right)}=0.4\ /\ 2.5$$

in men and women, respectivily (Lozano et al 2007, 2010c).

3.3.2 Clozapine and olanzapine

Since the HPA axis regulation appears altered in patients with schizophrenia, its modulation may be relevant for the control of symptoms in schizophrenia and antipsychotic treatment response. Otherwise, cortisol can be used as surrogate of the $5HT_{2a}$ receptor blockade, the receptor that has manifested itself as the most important in the serotonergic regulation of HPA axis and, thus, can be used as Surrogate Marker for dosing antipsychotics that act predominantly on the serotonergic pathways (Marx & Lieberman 1998; Meltzer et al 2001; Morrow et al 1995). Moreover, the alteration of the HPA axis, induced by antipsychotic with capacity for serotoninergic antagonism, that bind strongly to receptors 5-$HT_{2a/2c}$, can be used to modulate the response of cortisol and, eventually, to suppress the axis and to cause a decrease of the corticotropin-releasing factor, CRF, and the adrenocorticotropin hormone, ACTH (Morrow et al 1995; Patchev et al 1994).

Clozapine and Olanzapine, a $5HT_{2a}$ antagonists, show strong affinity for some dopamine receptors, but weak ability to antagonize the D_2 receptor, a receptor that modulates the neuroleptic activity. Evidence has shown that cortisol levels achieved in individuals treated with olanzapine and clozapine are dose dependent and directly proportional to the plasma concentrations of these drugs, at the start of antipsychotic treatment and along it.

Not only Olanzapine and Clozapine have shown a dose-dependent effect on the plasma cortisol levels, Risperidone also has significant effects but less pronounced compared with Olanzapine and Clozapine, whereas, Haloperidol has more modest effects. Olanzapine and Clozapine produce a cortisol increases, Δ-delta, up to 4-5 times higher than those produced by Haloperidol, while, risperidone produces a cortisol increases almost 1.5 times greater than observed with Haloperidol. Therefore, antipsychotics dosage are suitable to be monitored by using cortisol plasma levels (Girdler et al 2001).

3.3.2.1 PK-PD model

Mechanistic-model. Clozapine and Olanzapine, among other antipsychotics, cause an increase plasma cortisol levels in a dose-dependent manner, so the daily dosage has to be increased or decreased in order to reach cortisol plasma levels of 19.6 ± 6.6 mcg / dL and 18.3 ± 5.3 mcg / dL, the Clinical Surrogate Endpoint for Clozapine or Olanzapine, respectively (Lozano et al 2007, 2008a, 2010c, 2011a).

Once the steady-state and a pharmacological response, ranging between the 20-80% of maximal effect, is reached, we can estimate the optimal dose required to achieve cortisol values of 19.6 ± 6.6 mcg / dL and 18.3 ± 5.3 mcg / dL, the Clinical Surrogate Endpoints for Clozapine or Olanzapine, respectively, using equation 2 (Lozano et al 2008a, 2011a).

3.3.2.2 PK-PD model

Clozapine and Olanzapine are extensively metabolized in the liver, via the cytochrome P450 system, to polar metabolites suitable for its elimination in the urine and faeces. The CYP1A2 isoenzyme is primarily responsible for metabolism of Clozapine and Olanzapine , but another CYP`s seems to play a role, as well. Inducers agents, e.g. cigarette smoke, or inhibitor agents, e.g. Theophylline, Ciprofloxacin, Fluvoxamine, of the CYP1A2 may increase or decrease, respectively, the metabolism of Clozapine and Olanzapine. For example, the induction of metabolism caused by smoking means, that smokers would require double up the dose of Clozapine and/or Olanzapine compared with non-smokers ir order to achieve an equivalent plasma concentration (Entrez Gene 2011).

3.3.2.3 PD-PG model

The poblational analysis of plasma cortisol levels, using Kernel`s test , allow us to detect 2 populations, sex-linked and related to an alterations of the dopaminergic and/or serotonergic, caused by a combination of the different polymorphisms of genes encoding SERT and 5-HT_{2a} receptor, among others, obtaining from the application of the equation 2, the following equi-effective dose ratio:

$$\frac{\text{DOSE}\left(\text{genotype}:\text{wild type}\right)}{\text{DOSE}\left(\text{genotype}:\text{polimorphic type}\right)} = 2 \text{ or } 4$$

in dependence of the variant alleles present (Lozano et al 2008a, 2010c).

3.4 Methadone

The reduction of the testosterone levels induced by drugs with opioid activity, seems to be receptor mediated, since the different isomers have different activities: the levorotatory isomers are much more effective than dextrorotatory isomers (Cicero et al 1974, 1975, 1976, 1977; Mendelson et al 1976).

There are many different studies showing that the relative potency of drugs to reduce serum testosterone levels is parallel to its analgesic activity and its affinity for opioid receptors in the brain. So, this ability to decrease plasma testosterone and/or urine can be used as a trial to evaluate the structure-activity relationship, kinetic constants of association-dissociation to receptors, and reach conclusions about their pharmacological potency and its optimal therapeutic dose (Cicero et al 1975, Mendelson et al 1976).

The ability of opioid drugs to reduce serum testosterone levels, also, can be effectively used as a measure to assess the pharmacological activity of Methadone. Therefore, indirect assessment of the Methadone concentration in the biophase, can be accomplished by using the test of depletion of testosterone or test of depletion of LH that, also, seems to be specific for narcotic effect and correlates well with changes in testosterone levels (Kosterlitz & Warp 1968; Lozano et al 2008b, 2009b; Snyder 1975).

3.4.1 PK-PD model

Methadone, among other opiate drugs, causes a decrease in the value of index, testosterone/creatinine in urine, in a dose-dependent manner. We can dose Methadone by increasing o decreasing the daily dosage to reach index values of 20-30 mg / g, the Clinical Surrogate Endpoint. (Lozano et al 2008b, 2009b).

Once the steady-state and a pharmacological response, ranging between the 20-80% of maximal effect, is reached we can estimate the optimal dose required to achieve its Clinical Surrogate Endpoint, using equation 2

3.4.2 PK-PG model

Poblational analysis of the index, testosterone/creatinine in urine, using Kernel`s test , have allowed us to detect 3 different populations, as a result of combination of the different polymorphisms affecting the genes that encode CYP3A, CYP2B6, and NAT2, obtaining from the application of the equation 2, the following equi-effective dose ratio:

$$\frac{\text{DOSE}\left(\text{genotype}:\text{wild type}\right)}{\text{DOSE}\left(\text{genotype}:\text{polimorphic type}\right)} = 2 \text{ or } 4$$

in dependence of the variant alleles present (Lozano et al 2008b, 2009b).

3.5 Lamotrigine

Lamotrigine is a drug specifically used for epilepsy but also is effective as a mood stabilizer in treating bipolar depression, one of the most intractable stages of this disorder. Its iatrogenic effects, rare but extremely serious, such as Stevens-Johnson syndrome or Lyell syndrome, usually appear at 2-8 weeks of starting treatment. With unknown mechanism of action, it is believed that acts on sodium channels, its use is reserved for prevention of depressive episodes in bipolar disorder.

Lamotrigine is eliminated from the body by the action of the UGT1A4 enzyme, competing with bilirubin for the formation of their respective conjugates with glucuronide acid. Taking advantage of this interaction over UGT1A4, we can use bilirubin plasma levels as a indicator of plasma Lamotrigine concentration (French 2004; Lees & Leach 1993; Pellock 1999; Ramsay et al 1991; Rogawski & Löscher 2004).

The influence of bilirubin and other inhibitors of the UGT1A4 enzyme, on plasma concentrations of Lamotrigine, is calculated assuming a Michaelis-Menten kinetics, using equation 4, and a competitive inhibition model, as follows:

$$\Delta[Ltg] = \frac{\Delta[Bil]}{[E_o]^2 K_{M_{Ltg}} K_{M_{Bil}}} \quad (6)$$

(E_o = [UGT], K_M = Michaelis-Menten Constant)
(Bil= Bilirrubina, Ltg= Lamotrigina, Inh= Inhibidor)

allowing us to conclude that the main factors affecting Cp of Lamotrigine are the amount of UGT enzyme (Eo) and K_M values of inhibitors with respect to those of Lamotrigine and Bilirubin, according to the following relation:

$$\frac{\Delta[Ltg]}{\Delta[Inh]} = \frac{K_{M_{Inh}}}{K_{M_{Ltg}}} \quad (7)$$

This method described above allows the analysis of the main factors affecting competitive inhibition between two substrates, such as: UGT enzyme concentration, exponentially, and K_M value of substrates (Lozano et al 2009a, 2009b, 2010d).

3.5.1 PK-PG model

Is based on individual genetic polymorphisms which can alter the enzymatic activity of UGT1A1: The enzyme that conjugates bilirubin is called uridindifosfoglucuronato glucuronosyltransferase,UGT, and its production is regulated by a promoter that can have a mutation that causes decreased production of this enzyme. The amounts of UGT, in Gilbert's syndrome, are reduced until 30% of the normal value. The genetic defect is in the insertion of an extra base pair in the promoter TATA box in the gene encoding the enzyme UGT and that is located on chromosome 2 (Bosma et al 1995). Gilbert's syndrome, therefore, is a disease in which there is a high bilirubin level and the values in these patients ranging between 20 mmol/dl and 80 mmol/dl, obtaining from the application of the equation 6, the following equi-effective dose ratio for Lamotrigine:

$$\frac{\text{DOSE}\ (\text{genotype}: \text{wild type})}{\text{DOSE}\ (\text{genotype}: \text{Gilbert`s syndrome})} = 2$$

(Lozano et al 2009a, 2009c, 2010d).

3.6 New antiepileptics

The new generation of AEDs such as Topiramate, Oxcarbazepine, Gabapentin, and Levetiracetam, acts by enhancing GABAergic neurotransmission: The gamma-aminobutyric acid, GABA, has 2 types of receptors, A and B. When GABA binds to $GABA_A$ receptor, facilitates the passage of chlorine, negatively charged ion, inside the cell through chloride channels. This influx of chloride increases the negativity of the cell (ie, a resting potential more negative membrane) causing it a greater difficulty to reach the action potential resulting, finally, in a cell stabilization (Barnard et al 1998; Kravitz et al 1963; Krnjević & Schwartz 1967; Sieghart & Sperk 2002; Takeuchi & Onodera 1972; Takeuchi & Takeuchi 1967, 1969).

The GABAergic transmission, may be increased or facilitated, by direct binding of an agonist, such as progesterone, benzodiazepines, barbiturates, to the $GABA_A$ receptors and its subsequent activation; by blocking the presynaptic uptake of GABA by Tiagabine; by inhibiting the metabolism of GABA by GABA-transaminase, such as Vigabatrin and Valproate, or by increasing GABA synthesis modulating the enzyme glutamic acid decarboxylase, GAD, responsible for the decarboxylation of glutamate to GABA, as is the case of Gabapentin and other AEDs that enhance the production of GABA and causes a down-regulation of glutamate. For Felbamate, whose exact mechanism is unknown, it is known that exerts its effect on the GABA receptor and by antagonizing the NMDA receptor, while, Topiramato locks the sodium channels of voltage-gated and increases the activity of GABA through the activation of some subtype of GABA receptors, antagonizing some subtype of glutamate receptor and inhibiting the enzyme carbonic anhydrase, particularly isozymes II and IV (Kapetanovic et al 1998; Kume al 1994).

The GH plasma levels, also, have been used as a Surrogate Marker of noradrenergic transmission and, more recently, as evidence of $5HT_{1a}$ and $5HT_{1b/d1}$ receptor activation, being this another example of how one Surrogate Marker serves as measure for very different effects in the CNS (Dinan 1996; Facchinetti et al 1994; Herdman et al 1994; Laakman al 1990; Mota et al 1997).

3.6.1 PK-PD model

The GH plasma levels, can serve as a Surrogate Marker for assessing the GABAergic transmission in the CNS and is therefore a useful tool for dosage regimen calculation of the new antiepileptic drugs and for the right choice of therapeutic strategy, since, the oral administration of drugs that facilitates GABAergic transmission, among them the antiepileptics, cause a rise of growth hormone plasma levels, GH, in a dose-dependent manner, being GH release induced by gamma-aminobutyric acid, GABA, and mediated by a dopaminergic mechanism, via dopamine release at suprapituitary level (Cavagnini et al 1980a, 1980b; Powers et al 2008).

Thus, eg, Diazepam administration causes a dose-dependent rise in GH and the reached plasmatic peak is related to the plasma level of the drug. This highly significant correlation of the serum concentrations, between GH and Diazepam, has been found, also, with other AEDs, that act via the release or facilitation of GABAergic transmission, so we can use the plasma levels of GH as a Biomarker for dose adjustment of Diazepam, Topiramate, Gabapentin, Oxcarbazepine, Valproate and Levetiracetam, being the optimal dose, that which allow us to achieve the Clinical Surrogate Endpoint of GH equal to 15-25 ng/ml (Monteiro et al 1990; Monteleone et al 1987; Syvälahti & Kanto 1975).

Once the steady-state and a pharmacological response, ranging between the 20-80% of maximal effect, is reached we can estimate the optimal dose required to achieve the Clinical Surrogate Endpoint of GH equal to 15-25 ng/ml, using equation 2.

4. Conclusion

In this chapter, we have developed some PK, PD and PG models , in order to study and monitor the effectiveness, dosage regimen calculation and security of drugs used in psychiatry, by means of Biomarkers of drug concentration in biophase and the incorporation

of all the most innovative techniques in pharmacokinetics, pharmacodynamics and pharmacogenetics , which allow us to:

1. Estimate their pharmacokinetic and pharmacodynamic parameters, using for this purpose, PK-PD, PK-PD and PG-PG modelling, and quantitative analysis of dose-effect relationships with mathematical covariant techniques.
2. Quantify the effect of different genetic polymorphisms of CYP450, receptors and carriers, in dosage regimen calculation of different drugs above described.
3. Identify, using Kernel`s test, the different phenotypes and subpopulations originated in the different dose-response and metabolic behavior, such as the EM, PM and UM phenotypes.

In conclusion, the use of Biomarkers in PK, PD and PG modelling, in continuos developing, has provided us with the adequate tools to choose the best therapeutic strategy and calculate optimal dose, in order to improve the therapeutic drug monitoring of psychiatric drugs, relapses, drug side effects and clinical outcome of the most common psychiatric diseases. http://cpmc.coriell.org/Sections/Medical/DrugsAndGenes_mp.aspx?PgId=216.

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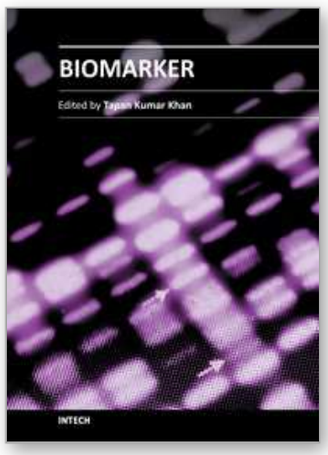
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Clinicians, scientists, and health care professionals use biomarkers or biological markers as a measure of a person's present health condition or response to interventions. An ideal -biomarker should have the following criteria: (I) ability to detect fundamental features of the disease, (II) ability to differentiate from other closely related diseases, (III) ability to detect early stages and stages of progression, (IV) the method should be highly reliable, easy to perform and inexpensive, and (V) sample sources should be easily accessible from body. Most of the chapters in this book follow the basic principle of biomarkers.

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