Gender based psychopharmacology: gender influence in the pharmacological treatment of mental disorders

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Psicofarmacología sensible al sexo: influencia del sexo en el tratamiento farmacológico de los trastornos psiquiátricos

Summary

Gender-based pharmacology is a new research and clinical area which could be defined by the inclusion of gender-related variables in clinical, research and educational issues with respect to pharmacotherapy.

Most of the studies which have studied pharmacokinetic gender differences in psychotropic drugs have found that women tend to have higher plasma concentrations.

As regards differences in treatment response, most evidence points to a more rapid response to neuroleptics and lower therapeutic doses in women, and, on the other hand, a possible better response to selective serotonin reuptake inhibitors (SSRI) in premenopausal women.

In addition, women appear to have a higher incidence of adverse effects to different psychotropic drugs.

Key words: *Gender differences in the pharmacokinetics. Gender differences in treatment response. Gender differences in adverse side effects.*

Resumen

La farmacología sensible al sexo es una nueva área de estudio que se podría definir como la que incorpora conocimientos de variables relacionadas con el sexo en las decisiones clínicas, de investigación y de docencia en farmacoterapia.

La mayoría de trabajos que han estudiado las diferencias farmacocinéticas de los psicofármacos en función del sexo han hallado que las mujeres presentan concentraciones plasmáticas más elevadas.

Por lo que respecta a las diferencias en respuesta al tratamiento farmacológico, los datos más contrastados son una respuesta a los neurolépticos más rápida y a dosis más bajas en las mujeres y una posible mejor respuesta en las mujeres en la premenopausia a los inhibidores selectivos de la recaptación de serotonina (ISRS).

También las mujeres parecen presentar con más frecuencia efectos secundarios a los diferentes psicofármacos.

Palabras clave: *Diferencias de sexo en farmacocinética. Diferencias de sexo en respuesta al tratamiento farmacológico. Diferencias de sexo en efectos secundarios.*

INTRODUCTION

Health differences in regards to sex and gender have not been debated and studied until recent decades. At present, there is growing interest in these subjects, mostly promoted by the need to avoid health inequalities of the different groups in society.

During the second half of the XX century, it was verified that most of the disorders or diseases were investigated in men and then the results were generalized without any critique to men and women, for their use in the clinical practice. It was also observed that the diagnostic and therapeutic resources used in a certain clinical situation were not the same in both genders[1]. A very important fact was that referring to the development of the different pharmacological treatments. Historically, women were excluded as experimental subjects in most of the pharmacology studies. Furthermore, many times, although men and women were included in the trials, the results were not analyzed considering gender. Since 1993, however, the Food and Drug Administration (FDA) has reviewed this question and recent guidelines recommend that clinical trials on the development of new drugs be analyzed considering the differences in gender and that factors related with the effects of the menstrual cycle and the sexual hormones in the drugs should be studied[2].

In this content, the so-called gender sensitive pharmacology has appeared. This new study area could be defined as that which incorporates knowledge of variables related with gender in the clinical, research and teaching decisions in pharmacotherapy.

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Although at present there are still few studies that have taken the gender factor into account when studying pharmacokinetics and pharmacodynamics of the different psychodrugs, the results found point to the fact that future studies could change the way psychodrugs are administered, considering gender and the effects of the endogenous and exogenous reproductive hormones, as presently occurs with age[3].

PHARMACOKINETIC GENDER DIFFERENCES OF THE PSYCHODRUGS

General pharmacokinetic differences

Absorption

Some of the most contrasted pharmacokinetic differences are slower gastric emptying in premenopausal women than in men. The differences in intestinal transit have not been so contrasted, but point to a faster transit in women. These two factors could result in lower absorption in women. However, baseline gastric acid secretion is markedly less in premenopausal women and although this pharmacokinetic effect has not been directly demonstrated in psychodrugs, it does suggest greater gastric absorption of the basic substances (tricyclic antidepressants, benzodiazepines) in women and thus, larger concentrations in plasma[4,5].

Distribution

The most important differences are related with the fact that women tend to have lower weight, lower blood volume and greater percentage of body fat. Although the first two factors mentioned may contribute to higher levels of drugs in blood, a higher percentage of fat is associated to greater distribution volume and lower concentrations[5]. Lipophilic substances such as benzodiazepines tend to accumulate in the fatty tissue and this fact may mean an accumulation and prolongation of the half life of these drugs in women, above all in the elderly, because age increases fatty tissue[5].

Women have higher brain flow than men, especially during the second and third decades of life[6].

The data on differences in fixation of the different drugs to plasma proteins are not consistent, although there are some studies that indicate that women may have lower fixation of the drugs to proteins[5].

Hepatic metabolism and elimination

Oxidation reactions seem to be more sensitive to the gender effects than those of conjugation[7], but both reactions are slower in women than in men and this leads to less clearance and higher plasma concentrations in women.

Gender differences have been identified for several isoenzymes of the cytochrome P450 system. The most relevant differences are those that affect CYP3A4 isoenzyme that makes up more than 60% of the total P450 content in the liver. This isoenzyme is influenced by gender and age. Young women have greater activity of this isoenzyme than men and postmenopausal women. Thus, young women have lower levels of benzodiazepines[8]. This isoenzyme also participates in the metabolization of fluvoxamine and nefazodone. Women have a higher activity of CYP2C19 isoenzyme than men. Imipramine, chloripramine, citalopram and diazepam are metabolized primarily by this and thus, there may be lower concentrations in women than in men who receive the same doses[9]. There is also some evidence that CYP1A2 activity may be less in women[9]. The isoenzyme participates in metabolization of fluvoxamine, clozapine and tricyclic antidepressants.

Regarding the gender differences in elimination, renal clearance is less in women, due to lower glomerular filtration[5].

In conclusion, although the findings on differences in pharmacokinetics of psychodrugs based on gender are still preliminary and offer results that are sometimes contradictory, most of the studies that have reviewed these data have concluded that women would tend to show higher psychodrug plasma concentrations than men[4,5].

In any event, little is still known on the possible gender differences in the drug concentration in the central nervous system.

Effects of synthetic hormones in psychodrug pharmacokinetics

The results of different studies suggest that hormonal contraceptives may cause changes in psychodrug absorption in that it minimizes the gender differences observed. Hormone treatment used in menopausal women, on the contrary, preserves the gender differences in the absorption observed in premenopausal women. In addition, exogenous estrogens and progesterone decrease gastric acid secretion[5].

Regarding effects on metabolism, in general, contraceptives (OC) tend to reduce clearance for drugs metabolized by oxidation and increase that of those metabolized by conjugation[7].

In addition, OC reduce the activity of CYP1A1/2 hepatic isoenzymes and this fact may cause an increase in the plasma levels of tricyclic antidepressants such as imipramine and clozapine[10].

There is little data that study the effects of hormone replacement therapy in psychodrugs. The estrogens used in this treatment are metabolized by the CYP3A4 isoenzyme and given that fluvoxamine, fluoxetine and nefazodone inhibit the activity of this isoenzyme, it may be necessary to decrease the estrogen doses[9].

Pharmacokinetic changes during the menstrual cycle

The plasma concentrations of some psychodrugs may have fluctuations during the menstrual cycle. Oxidative

metabolism has a peak in the middle of the cycle and thus the drugs using this pathway have greater clearance in this cycle phase[11].

Metabolism of antidepressants seems to decrease the follicular phase, has a peak during ovulation and remains relatively high during the luteal phase[8]. For practical effects, the plasma concentrations, and perhaps adverse effects, may increase during the follicular phase. Reductions during the luteal phase may be associated to a decrease in efficacy or relapse. These menstrual effects seem to be more pronounced in the subgroup of women who suffer dysphoric premenstrual symptoms[5].

Studies on possible changes in lithium levels during the menstrual cycle offer contradictory results, but they may affect the evolution of the bipolar disorder in some cases[12].

PHARMACOKINETIC DIFFERENCES FOR THERAPEUTIC GROUPS

Benzodiazepines

The studies that have investigated gender pharmacokinetic differences of benzodiazepines (BZD) found that the most relevant data were that the clearance of benzodiazepine metabolized by conjugation (lorazepam and oxazepam) seems to be slower in women than in men[13] while that of benzodiazepines metabolized by oxidation does not seem to have gender differences[14].

Although there are studies that have found gender differences in the metabolism of alprazolam, these are not very consistent. The maximum concentrations of this drug are higher in women, but this finding seems to be more related with weight differences than with gender. In addition, no changes were found related with the menstrual cycle in the concentrations of this drug[15].

Interactions of BZD and hormonal OC are a factor to be considered. In general, OC inhibit metabolism by oxidation and facilitate metabolism by conjugation[7]. These changes may make dose readjustments necessary.

Antidepressants

The antidepressants studied most in regards to differences in gender is imipramine. A review study of Hamilton and Grant[16] on pharmacokinetics of imipramine in relationship with gender differences shows that women over 50 years have higher dose adjusted plasma levels than men. In younger women, these differences are more controversial.

Some studies with chlorimipramine also show higher levels in women[17]. A study with sertraline[18] also found higher levels in young women than in young men.

Some antidepressants may show variations in plasma concentration during the menstrual cycle. In the leuteinic phase, the desipramine and trazodone plasma levels show important decreases, above all in women with premenstrual syndrome[19].

One study that investigated interactions between hormonal OC and imipramine found that the former decrease hepatic metabolism of this drug and produce an elevation of the imipramine levels. Because of these results, it is recommendable to reduce imipramine doses in women who take OC over a long period by 2/3 in regards to those who do not take them[10].

Neuroleptics

Few studies have compared antipsychotic blood levels in relationship with gender. Most of the results point to higher concentrations in women[20].

Effects of the OC on the pharmacokinetics of neuroleptics are not known.

Lithium

Although there are few studies that examine this question, it seems that women have less lithium clearance and present more variations, in some cases associated to the menstrual cycle[21].

Carbamazepine

Carbamazepine is a potent hepatic inductor and may reduce the efficacy of the OC and replacement hormone[22].

The gender differences described may be important, above all, in the drugs in which the plasma concentrations clearly correlate with efficacy and side effects. There is evidence that when there are bioavailability differences of the drugs between women and men, the optimum doses that have been obtained in dose studies performed, above all, in men, may be too high for women. If this factor is not taken into account, women may be subjected to an increased risk of side effects[20]. In fact, there are studies that find that women experience growingly more serious side effects due to antidepressants and antipsychotics than men[23].

In summary and although the data on pharmacokinetic differences are still scarce, it can be concluded that when pharmacological treatment is established, it is necessary to keep in mind that women may present side effects at the usual doses more frequently and that, the need to adjust the medication in the menstrual period and when sexual hormones are administered should be considered on an individual basis.

GENDER DIFFERENCES IN THE RESPONSE TO TREATMENT WITH PSYCHORUGS

Gender differences in the response to antidepressants

There has been little specific study of the gender differences in response to antidepressant treatment. In a meta-

analysis of the studies published between 1957 and 1991 that recorded response to imipramine based on gender (35 studies that included 342 men and 711 women), men responded better to it than women[24]. An interesting study is that published in 2000 by Kornstein et al. who examined the gender differences in response to treatment comparing imipramine and sertraline in a large group of patients (400 women and 235 men) with major chronic depression and double depression[25]. The results show that premenopausal women respond worse to tricyclics than men, and seem to respond better and faster to selective serotonin reuptake inhibitors (SSRI); while men respond better to imipramine. It has also been found that the better response of premenopausal women to the SSRI is not maintained after menopause[25,26]. These differences may be related with the theory that estrogens increase the down-regulation induced by antidepressants on the 5HT2 receptors[27].

An efficacy comparison study between fluoxetine and maprotiline also found that premenopausal women respond better to fluoxetine than to maprotiline[28].

Few studies have analyzed the possible gender differences in the combined treatment of depression (antidepressants and psychotherapy). One study performed by Thase et al. based on a meta-analysis of six studies found that there were no differences in response between combined treatment or psychotherapy alone (interpersonal or cognitive) in women under 40 years of age. However, men responded better to combined treatment than to psychotherapy in all the age groups. Women over 50 responded similarly to men. This result could be explained by the lower response of the premenopausal women to tricyclics[29].

In regards to potentiation treatments of antidepressants, potentiation with thyroid hormone seems to be more effective in women than in men[30]. The studies that have analyzed the effect of estrogens as a coadjuvant treatment of depression have generally obtained negative results[3]. The most promising results have been found in the treatment of post-partum depression and premenstrual dysphoric disorder. Estrogens also seem to be useful in the treatment of depressive symptoms during menopause, although the best results have been obtained in women with surgical menopause and in mild and moderate symptoms. In a study performed with elderly women with depression who received fluoxetine, a positive interaction was found between addition of estrogens to the treatment and therapeutic response[31].

The few studies that have evaluated the differences in response to electroconvulsive treatment (ECT) have found that women seem to require lower electrical stimuli. In addition, women seem to have less cognitive dysfunction than men with right unilateral ECT, surely due to the sexual differences of lateralization[32].

Gender differences in response to mood stabilizers

There are few studies on the gender differences in response to mood stabilizers. Viguera et al. analyzed the results of 17 studies that made it possible to assess the differences in response to lithium in patients with major affective disorder based on gender, and they did not find any significant differences in the short or long term response rate[33].

A study on valproate efficacy in bipolar disorder found that men responded better than women to the effects of prophylaxis of depressions[34].

Gender differences in response to antipsychotics

Most of the studies performed on differences of response to treatment have been performed with typical or first generation antipsychotics and suggest that young women require lower doses of medication than men[35,36], while postmenopausal women require higher doses than men[37]. One of the possible explanations of these differences is changes in estrogen levels[38].

Many studies found that women with schizophrenia respond more rapidly and have a higher response index to typical antipsychotics than men[35,37,38]. In a study of patients with a first episode, Szymanski et al. found that 87 % of women and 55 % of men achieved symptom remission after 20 weeks of treatment[35].

Few studies have been performed with atypical antipsychotics, but it seems that gender differences are less relevant. Some studies suggest that women respond worse to clozapine than men[39,40], but these studies were in refractory patients. Perry, on the other hand, did not find differences with clozapine[41].

One study that compared response to olanzapine and haloperidol between women and men with schizophrenia found that women responded better than men to olanzapine regardless of the duration of the disease and that, in addition, premenopausal women responded better than post-menopausal ones to both haloperidol as well as olanzapine[42].

One study that examined response to risperidone based on gender, however, did not find any differences[43].

The differences in response to treatment may be due to other non-pharmacological factors, that must be taken into account. Tobacco may decrease antipsychotic levels in plasma. Goff[44] found that schizophrenic men smoked more (85 %) than schizophrenic women (47 %) and that those who smoked received higher doses of antipsychotics. Salokangas[45] found that the daily doses of antipsychotics increased with age in patients who smoked, but decreased with age in the non-smokers, without gender effect on the dose.

Drug compliance is another factor that may influence the differences in response found. Different studies find that men are less compliant[46,47]. Others, on the contrary, do not find differences[48].

DIFFERENCES IN GENDER AND SIDE EFFECTS OF THE PSYCHODRUGS

Side effects of antipsychotics

Incidence and severity of side effects of antipsychotics show differences in regards to gender.

Most of the studies coincide that extrapyramidal symptoms secondary to treatment with neuroleptics are more frequent in women[49]. In one study of patients with a first episode, Szymanski et al. found that women presented dystonia episodes more frequently (48% in women and 22.2% in men), but they did not find gender differences in the frequency of akathisia[35].

In regards to tardive dyskinesia, many studies have found that it is more frequent in women than in men. However, it seems that there are no differences in the frequency of tardive dyskinesia in patients under 50 years of age and that, the prevalence in women is greater than in men in patients between 50 and 70 years of age and the frequency continues to increase in the women after 50 years of age[50].

Women under treatment with clozapine also suffer agranulocytosis and eosinophilia more frequently than men[51].

Elevation of prolactin secondary to typical neuroleptics and to risperidone is also more frequent in women and this increases the risk of galactorrhea, amenorrhea and sexual dysfunction[52,53].

Side effects of antidepressants and mood stabilizers

Fewer studies have evaluated the side effects of antidepressants and mood stabilizers based on gender.

The sexual side effects have been studied the most. One study of Piazza[54] found that sexual dysfunctions during depression are more frequent in women and that women improve sexual activity more than men with SSRI treatment. Other studies, however, find that sexual effects due to SSRI in women are frequent[55].

Regarding treatment with lithium, most of the studies find that hypothyroidism in patients under treatment with lithium is more frequent in women than in men[56,57].

Furthermore, one study found that 45% of the women who took valproate had menstrual disorders and that there was an elevated risk of polycystic ovary and hyperandrogenism in women who began the treatment before age 20[58]. When choosing a prophylactic treatment in women, it is also important to consider that carbamazepine may reduce the efficacy of hormone treatments (especially oral contraceptives).

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