ABSTRACT OF PhD THESIS

THE STUDY OF SOME ANTIDEPRESSANTS AND ANTIPSICHOTICS IN PREGNANCY AND BREASTFEEDING

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Aims: The purpose of this thesis was to study the safety of the most commonly used antidepressants and antipsychotics during pregnancy and breastfeeding. Animal models (rats and sheeps) were used as for ethical reasons these studies cannot be conducted in humans. The class of selective serotonin reuptake inhibitors (fluoxetine, citalopram) and atypical antipsychotics (olanzapine, risperidone) were studied.

Material and method: Because there is no conclusive evidence from animal studies regarding the safety of these drugs during pregnancy, how medication is affecting the gestation in Wistar rats, by determining the number of uterine implantation, the embryotoxicity (number of uterine resorptions, classified as early or late depending on the absence or presence of placental remnants) and the fetotoxicity (the number of live fetuses, dead fetuses or fetuses with developmental abnormalities) was evaluated. To confirm the presents of resorbtions the uterine remnants were removed and analyzed histopatologicaly.

Body weight changes in experimental groups were monitored at the end of each therapy week throughout the entire gestation period and compared with those of a control group.

Because of ethical reasons it is difficult to evaluate the transfer of these psychotropic drugs into human milk that's why an animal model was developed to assess the blood / milk rate transfer after repeat doses, to calculate the relative infant doses (using the maternal weight-adjusted doses) and to measure drugs serum and milk concentrations, in order to correlate the pharmacokinetic (milk/plasma ratio, infant plasma levels) and pharmacodynamics data (side effects in breastfed infant).

Results:

Body Weight Changes

Weight gain was significantly increased at the end of gestation compared to their initial weight in animals treated with antidepressants. However an initial body weight loss was observed in both fluoxetine (20 mg/kg body weight) and citalopram (3 mg/kg body weight) groups. This can be explained by a decrease in food consumption consequence of treatment with SSRIs. They increase the concentration of serotonin in the central nervous system as a result of the inhibition of neurotransmitter reuptake from the synaptic cleft contributing to an anorexic effect.

In the antipsychotic groups (olanzapine 6 mg/kg body weight, risperidone 3 mg/kg body weight) the weight was significantly increased compared to their initial weight at the end of the gestation, although in the last week of therapy there was a decrease in body weights. The increase of body weight was predictable because due to serotonin receptors blockade these substances are increasing food intake, a phenomenon that overlapped with the gestation period.

The Macroscopic Evaluation of Uterine Content

The use of SSRI's and atypical antipsychotics during gestation in white Wistar rats affected the gestation in different evolutionary stages.

The results of these preclinical studies suggest that among antidepressants, fluoxetine is the safest to be administered during this period. Even though after fluoxetine administration uterine resorptions were identified, the statistical analysis of results suggested that there is no significant difference between the control group and drug treated animals regarding the total number of accidents or the total number of resorption; while there were statistically significant differences in citalopram group versus control group. But comparing the two studied antidepressants there were no statistically significant differences.

Although there were no statistically significant differences between the two antipsichotics, when comparing them with the control group, the results were statistically significant for the total number of accidents and the number of resorption. However, taking into account the macroscopic evaluation of uterine contents we concluded that olanzapine is less harmful than risperidone.

HPLC/MS/MS Analytical Method Development and Validation for the Determination of Active Substances from Plasma and Milk Samples

HPLC/MS/MS analytical methods to investigate the transfer of substances through the blood/milk barrier were developed and validated. The methods can be used for bioanalytical studies using plasma or milk samples.

The Excretion of Drugs into Milk

An animal model (sheep animal model) was created to investigate the drug penetration across the blood-milk barrier. Experimental results suggest a limited transfer for fluoxetine - 20 mg daily (norfluoxetine) and olanzapine - 5 mg daily, the milk/plasma ratio (M/P) being <1 (are considered compatible with breastfeeding the substances presenting a M/P ratio <1). In addition, the relative infant dose was lower than 10% of the maternal weight-adjusted dose.

Because no adverse effects were noted in breastfed lambs and the serum concentrations detected in these show a benefit/risk ratio favorable to this medication.

After citalopram - 20 mg daily - the M/P ratio obtained was > 1, which means that it should be avoided during breastfeeding. However because no obvious adverse reactions were noted in lambs (suckling difficulties, sedation, bowel movements changes), low serum concentrations detected in them, the high therapeutic index of citalopram and the potential risk of the treated condition reflects a benefit that it is believed to be favorable to the medication despite the high milk transfer (milk/plasma ratio being situated at the borderline between significant/ negligible exposure of the infant).

The safety of risperidone -2 mg daily during breastfeeding was difficult to assess because the concentration of 9-hydroxy-risperidone in plasma and milk samples could not be quantified. But because the activation of risperidone to 9-hydroxy risperidone depends of CYP2D6 enzyme activity which is deficient in children (in this case - lambs) and risperidone hasn't been identified in milk it is considered that it might be used during breastfeeding.

Conclusions: Pharmacokinetic interspecies extrapolation (in this case sheep $\Rightarrow$ human) is often difficult because for ethical reasons further evaluation of such results in controlled clinical trials can't be done and must be viewed with caution, but it is mandatory, and imposed by the international guidelines and the regulatory authorities for medicines.

Keywords: antidepressants, antipsychotics, gestation, uterine resorptions, breastfeeding.