DOCTORAL THESIS
ABSTRACT
RESEARCHES UPON METABOLICAL AND HISTOPATHOLOGICAL CHANGES PRODUCED BY CERTAIN ANTIPSYCHOTICS IN ANIMAL

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CRAIOVA
2011
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KEY WORDS: antipsychotics, rats, side effects, leptin, metabolic syndrome, liver, kidney
INTRODUCTION

The issue of antipsychotic drugs represents an important moment in the development of psychiatric care, both from the point of view of clinical evaluation and therapeutic dimension.

If, from the perspective of clinical efficiency, conventional antipsychotics lived up to expectations, side effects and long-time monitoring leaded these substances in the second line therapy of psychotic disorders.

After 1990, the issue of second-generation antipsychotics, atypical antipsychotics, was considered a true revolution in psychopharmacology.

From clinical point of view, atypical antipsychotics are a heterogeneous group of substances characterized by a superior efficiency against negative, positive and affective symptoms in schizophrenia and by an adequate cognitive protection. Side effects profile was an important element which leaded these substances in the first line of treatment of psychotic disorders.

However, sufficient data emerged warning about the risk of side effects and imposing a clinical and biological monitoring of patients under therapy with atypical antipsychotics. Complex interdisciplinary evaluations are necessary both on short and long time.

In this study, we aimed to achieve an experimental study upon rats, to show eventual side effects of those substances, using conventional antipsychotics (haloperidol, chlorpromazine and haloperidol decanoate) and atypical antipsychotics (aripiprazole and risperidone).

MATERIALS AND METHODS

We used experimental animal model: adult male Wistar rats, weighting 225-240 g with age range 70-80 days. The experiment lasted for four weeks. We used 42 animals divided in six groups according with the administered drug:

- Chlorpromazine group: seven animals labeled from C1 to C7;
- Haloperidol group: seven animals labeled from H1 to H7;
- Haloperidol decanoate group: seven animals labeled to HD1 to HD7;
- Aripiprazole group: seven animals labeled from A1 to A7;
-Risperidone group: seven animals labeled from R1 to R7;
-Control group: seven animals labeled from M1 to M7.

The animals were kept in individual separate labeled cages, well ventilated with 12 hours light/dark alternation at a temperature 25 +/- 1 C. Feeding was achieved by standard food (granulated compound feed, a complete provender for laboratory mice, rats or hamsters by „Cantacuzino” Institute, from Bucharest and fabricated at Baneasa Station) and water at libitum.

For each animal, there was a unique record file. The weight was measured and recorded a jeun, in the morning, between 9:00 and 10:00 and was used for adequate dosing of the drug. All substances were injected.

Twenty-four hours from the last drug administration, the animals were put to sleep with ethyllic ether and sacrificed and the liver and the kidney and were harvested. A blood sample was also drawn for biochemistry: glycemia, cholesterol, triglycerides, leptin, GOT, GPT, urea and creatinine. Salivary leptin was determined by the ELISA technique on the five groups of rats treated with antipsychotics, to evidence the salivary leptin levels registered before and after neuroleptics administration.

Harvested organs were fixated in 10% formalin solution for 36-48 hours and prepared by paraffin inclusion technique to obtain blocks of tissue. Those were cut with microtome obtaining slices of 4-5 um, stained with Hematoxylin-Eosin (for overview and detailed histologic imaging), trichromic Goldner-Szekly (for unspecific stroma) and Gomory silver impregnation (for specific stroma, the reticulinic stroma).

One animal was found dead in the group treated with chlorpromazine in the 26th day of the experiment. Its liver and kidney was harvested for microscopic examination.

**RESULTS**

The results of the study of serum leptin was completed by the study of salivary leptin following any changes in the levels of salivary leptin before the first dose of drug and following the treatment with each of the investigated neuroleptics. The results’ values were expressed in ng/mg, and showed the growth of salivary and serum leptin’s concentrations between the start and the completion of the treatment, for each group taken in study, less for the aripiprazole group.
Body weight changed in every group of study between the first and the last day of the experiment. The weight increased for chlorpromazine and risperidone and diminished for aripiprazole, haloperidol and haloperidol decanoate.

Laboratory tests for glycemia, cholesterol and triglycerides have explored the possible metabolic syndrome. The results were expressed in mg/100ml blood for glycemia, and in <200 mg/dl for cholesterol and triglycerides. They showed: hyperglycemia for chlorpromazine and maximum values of glycemia for risperidone; very increased values of triglycerides for haloperidol and risperidone and normal values for the other three neuroleptics; normal values for cholesterol in every group of study, but the five groups injected with neuroleptics presented very low values in comparison with the control group.

For the liver function we tracked the changes of GOT and GPT, and for the kidney function we determined the values of serum urea and serum creatinine, in comparison with the control group, that had the same life conditions, but did not follow any neuroleptic treatment.

The aggressive action of antipsychotic drugs exerted upon liver parenchyma and stroma, but only in a more restricted manner upon the kidney’s morphology. Unspecific stroma is very little modified in the treated groups compared to the control group, and it is more affected in the group treated with chlorpromazine, including the animal deceased before the end of the experiment. The aspect of specific stroma presents changes in the quality and quantity of the reticulinic fibers. Sometimes the reticulinic stroma is profoundly altered, up to vanishing in certain areas corresponding to areas of hepatocitary necrosis.

The groups treated with haloperidol, haloperidol decanoate, risperidone and aripiprazole did not show the same intensity of morphologic changes noticed in the chlorpromazine group.

**CONCLUSIONS**

The studies have revealed mixed results between groups proving that the antipsychotics given behave differently from one group to another.

For the laboratory tests, minimum and maximum values had very small differences within each group.
From the five substances studied, it appears that metabolic side effects can be determined by chlorpromazine and risperidone, but not by aripiprazole.

We revealed a somehow bearable toxicity to two of the classic antipsychotics (haloperidol and haloperidol decanoate) and two from the recent generation (risperidone and aripiprazole) and a high toxicity of chlorpromazine, upon the liver's and kidney's morphology.

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