Contributions to the study of morphofunctional interrelations in the liver of the rats treated with certain antipsychotic drugs

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Abstract
The issue of antipsychotics in psychiatry constituted a revolution at the time. The firsts, starting with chlorpromazine represent the conventional antipsychotics, in the last decades there was a new generation of antipsychotics, atypical, which improved the results in treating psychoses. Because, as any drug, it may have adverse effects we aimed an experimental study on rats to observe the toxic potential on liver of both generations of antipsychotics. From the first generation we used chlorpromazine, haloperidol and haloperidol decanoate and from the second, aripiprazole and risperidone. Results of the study show an increased toxicity of chlorpromazine and diminished among the others, without being the same for every drug.

Keywords: antipsychotic drugs, liver toxicity.

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. For approximately 50 years, first-generation antipsychotics (typical, conventional) had a significant contribution in the treatment of psychotic disorders [1].

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 [2, 3].

After 1990, the issue of second-generation antipsychotics (atypical) 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 effect profile was an important element leaded these substances in the first line of treatment of psychotic disorders [4, 5].

Therapeutic properties of this group of antipsychotics are reflected by a good therapeutic compliance and an adequate level of patients’ quality of life.

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 [6, 7]. Complex interdisciplinary evaluations are necessary both on short and long term.

In this study, we aimed to achieve an experimental study upon rats, to show toxicity of those substances [8, 9], using conventional antipsychotics (haloperidol, chlorpromazine and haloperidol decanoate) and atypical antipsychotics (aripiprazole and risperidone) [10, 11].

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 from HD1 to HD7;
- Aripiprazole group: seven animals labeled from A1 to A7;
- Risperidone group: seven animals labeled R1–R7;
- Control group: seven animals labeled M1–M7;

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

For each animal, there was a unique record file. The weight was measured and recorded à 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 ethylic ether and...
sacrificed and the liver harvested. A blood sample was also drawn for biochemistry: glycemia, total cholesterol and triglycerides. Harvested organs were fixed 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 µm, stained with Hematoxylin–Eosin (for overview and detailed histologic imaging), trichromic Goldner–Szekely (for unspecific stroma) and Gömöry silver impregnation (for specific, reticulinic stroma).

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

**Results**

Liver is an organ consisting in parenchyma and stroma, but unlike other viscera, besides connective-vascular stroma (unspecific stroma) also presents specific stroma consisting in a highly ramified and anastomosed network of reticulin fibers (spongious-like stroma) (Figure 1). On this network, are disposed the cells (reticular cells), which generate specific stroma through their function of fibrogenesis.

We mention that this stroma is specific to hemolymphopoetic organs, and is particularizing them as structure, unspecific stroma being found in all organs.

Aggressive action of antipsychotics on liver determined a series of morphologic changes in all animals. It exerted upon the hepatocytary parenchyma and stroma (Figures 2–4) being determined both by the typical and the atypical antipsychotics.

**Figure 1 – Control group. Reticulinic stroma (Gömöri stain, ×100).**

**Figure 2 – Haloperidol group. Liver parenchyma (HE stain, ×200).**

At the level of parenchyma, the cellular changes had an aspect of granulo-vacuolar dystrophy. At the level of stroma, changes occurred in the porto-biliary spaces of Kiernan and in the specific stroma (Figures 5 and 6).

**Figure 3 – Risperidone group. Liver parenchyma (HE stain, ×200).**

Hepatocytary parenchyma presented granulo-vacuolar dystrophy in different stages of severity both in the groups treated with conventional antipsychotics and in the groups treated with novel antipsychotics.

The most advanced forms of granulo-vacuolar dystrophy up to hepatocytary necrosis were encountered in the group treated with chlorpromazine (Figures 4, 7 and 8).
Comparing morphologic results with laboratory data we observed a functional liver failure induced by chlorpromazine in the administered doses (Table 1).

Table 1 – *Laboratory data (range and average)*

<table>
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<tr>
<th>Group</th>
<th>Glycemia</th>
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<th>Tryglycerides</th>
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<td></td>
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**Discussion**

Toxic aggressive action of antipsychotic drugs exerted upon liver parenchyma and stroma. Upon liver parenchyma, toxicity is reflected by the granulovacuolar dystrophy observed inside every group of treatment but different from a group to another. In the chlorpromazine treated group, the aspect of the hepatocytary parenchyma is profoundly altered (Figure 4), pointing out the noxious activity of the drug compared to the other groups, including the control group.

The treatment with chlorpromazine determined, in the hepatocyte cytoplasm, especially periportal, lesions with dystrophic vacuolar aspect and even hepatocytary necrosis. Hepatocytes’ nuclei appear sometimes pyknotic, karyorrhexis, karyolysis, reaching total disappearance in the necrosed hepatocytes. Authors like Li J *et al.* [12], Gorrell MD *et al.* [13] and DeLeve LD *et al.* [14], in experimental animal studies demonstrated that periportal hepatocytes are more sensitive to toxic substances compared with anti-inflammatory activity in viral hepatitis, where the cytoplasmatic dystrophy seems to be located mainly in the pericentrolobular hepatocytes.

Comparing the general aspect in the HE staining of the rat’s liver in the chlorpromazine (Figure 4) treated group we found characteristic features comparative with the other groups (Figure 2, 3 and 9).

Unspecific stroma is very little modified in the treated groups compared to the control group. The stroma is more affected in the treated group with chlorpromazine, including the animal deceased before the end of the experiment. The change consists in the
increase of the porto-biliary spaces compared to the control group, increase determined by an increase in fibrocytes and a vascular congestion. A high quantity of connective fibers with tendency to interlobular expansion is equally noted.

Unlike viral hepatitis [13], which acts upon liver parenchyma in general but also upon the stellate cells in the specific stroma leading to the replacement of parenchyma with type IV collagen, reaching to a collagenisation of reticulin stroma and finally to liver cirrhosis [20–22], in our experiment (toxic type hepatitis), antipsychotics did not show the possibility to alter the metabolism of the collagen proteins producing cells.

Laboratory tests results show an alteration of the liver parenchyma corresponding to the toxicity of the five tested drugs. An increased toxicity was registered in animals in which chlorpromazine was administered compared to the other groups. Those presented various results for glycemia and triglycerides, differing from one group to another and from the control group, demonstrating thus the functional hepatocytary alterations following the aggression of antipsychotics, but in a more restricted manner than chlorpromazines.

The major functional deficit induced by chlorpromazine is demonstrated also by the fact that the deceased animal presented morphologic lesions similar to those observed in all chlorpromazine treated animals that survived to the end of the experiment.

**Conclusions**

In our experiment, which consisted in treating laboratory animals (male adult Wistar rats) with antipsychotics, three from the first-generation and two from the second, 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.

This high toxicity induced by chlorpromazine is demonstrated by the very advanced morphologic changes corresponding to the altered liver function reflected in altered laboratory tests results.

**References**


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