MANAGEMENT OF MARKED LIVER ENZYME INCREASE DURING OLANZAPINE TREATMENT:
A CASE REPORT AND REVIEW OF THE LITERATURE

Pauline Manceaux, Eric Constant, Nicolas Zdanowicz, Denis Jacques & Christing Reynaert
Université Catholique de Louvain, 5530 Yvoir, Belgium

SUMMARY
Objectives: Atypical antipsychotics commonly cause isolated asymptomatic increase in the aminotransferase levels. Furthermore, the strategy in the choice of antipsychotic agent must take into account hepatic tolerance because of the non-negligible incidence of liver disorders among the psychiatric population. The aim of this article is to better understand the strategy to adopt during an increase of liver enzymes in a psychotic patient under atypical neuroleptic treatment.

Method: A clinical case is presented of a female patient treated for psychotic decompensation with increase of liver enzymes (Olanzapine). Her treatment was changed several times over a period of 7 years and laboratory investigations were conducted simultaneously.

Results: It seems that the increase of liver enzymes is slightly more frequent with Clozapine and Olanzapine than Risperidone, Perazine and Haloperidol.

Conclusion: The different mechanisms of hepatotoxicity are unknown at present but it seems that the hypersensitivity mechanism is likely to be dose dependent. During an increase of enzymes, it is important to combine a control of hepatic enzymes with a reduction of neuroleptic dosage. Discontinuation should be considered if a continued increase of enzymes above certain values is shown or if a clinical symptom appears. We note also that some risk factors were found, including geriatric or pedopsychiatric age, obesity, and association with active ingredients or addictive substances responsible for hepatic disorders.

Key words: antipsychotic drug - side effect – olanzapine - hepatic tolerance

INTRODUCTION
Atypical antipsychotics commonly cause isolated asymptomatic increases in aminotransferase levels. Furthermore, the strategy in the choice of antipsychotic agent must take into account hepatic tolerance because of the non-negligible incidence of liver disorders among the psychiatric population. The aim of this article is to better understand the strategy to adopt during an increase of liver enzymes in a psychotic patient under atypical neuroleptic treatment.

METHOD
A 45 year old woman was admitted to hospital under the care of the psychiatry service for a psychotic disorder.

She had a history of steatosis but her preadmission laboratory investigations were normal. Her medications before hospitalization included Abilify 10mg daily, Solian 200mg twice daily.

Her medication history (Table 1):
- In 2005, she had been started on olanzapine at a 40mg daily dose. Labatory and liver enzymes were normal.
- In 2006, the laboratory results collected included an increase of liver enzymes.
- She stopped the olanzapine and started on clozapine.
- 2006-2008: Clozapine.
- 2009: the laboratory results collected included an increase of liver enzymes.
- She stopped the clozapine and started on amisulpiride.
- In 2010, she was admitted to hospital under the care of the psychiatry service due to increased delusions. Her regular antipsychotic medications were not continued after hospital admission and she stayed on olanzapine at a 10mg daily dose.
- In February 2010, the olanzapine was increased to a 20mg daily dose.

DISCUSSION
Thanks to this table, we can observe an important parallelism between the reintroduction of olanzapine and the increase of enzymes. In the literature, a decrease of the posology provokes an improvement of liver enzymes while its increase leads to an aggravation of liver enzymes (Ozcanli et al. 2006, Atasoy 2007).

In our case, the switch to another antipsychotic can improve the biology for a while.

Neuroleptic induced hepatotoxicity has rarely been reported in the literature, occurs via an unknown mechanism and results in liver biochemical abnormalities that are usually of no clinical significance (Table 2 and 3). For example: with approximately 30% to 50% of patient treated with clozapine, there is in an asymptomatic rise in serum aminotransferase levels (Chang et al. 2009). However, there are no current guidelines for routine monitoring of liver function tests and liver enzymes during its use.
Table 1. Results of laboratory investigations

<table>
<thead>
<tr>
<th></th>
<th>03/07</th>
<th>11/08</th>
<th>12/08</th>
<th>03/09</th>
<th>7/09</th>
<th>25/01/10</th>
<th>27/01/10</th>
<th>03/02/10</th>
<th>10/02/10</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASAT</td>
<td>43</td>
<td>16</td>
<td>56</td>
<td>42</td>
<td>26</td>
<td>27</td>
<td>32</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>ALAT</td>
<td>1</td>
<td>16</td>
<td>92</td>
<td>85</td>
<td>40</td>
<td>32</td>
<td>46</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>GGT</td>
<td>122</td>
<td>244</td>
<td>26</td>
<td>254</td>
<td>244</td>
<td>268</td>
<td>170</td>
<td>144</td>
<td>164</td>
</tr>
</tbody>
</table>

Table 2. On the hepaox website: above mentioned figures indicate for each pathology the number of available references in the literature

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Clozapine</th>
<th>Olanzapine</th>
<th>Risperdal</th>
<th>Quetiapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic increase in the aminotransferase levels.</td>
<td>27</td>
<td>15</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Cytolitic hepatitis</td>
<td>11</td>
<td>6</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Cholestatic hepatitis</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Steatosis</td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 3. Main cases of hepatic troubles under atypical neuroleptic treatment describle in the recent literature

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Liver diseases</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine: 300mg/day</td>
<td>The patient experienced lethargy and anorexia, and fever, eosinophilia, leukocytosis and abnormal liver parameters</td>
<td>Chaplin AC, Curley MA, Wanless IR. 2009</td>
</tr>
<tr>
<td>49 years old men</td>
<td>A retrospective review of 7263 treatment courses</td>
<td>Luo D et al. 2007</td>
</tr>
<tr>
<td>Olanzapine 150-300mg/day</td>
<td>It seems that the increase of liver enzymes is slightly more frequent with Clozapine in comparison with pérazine, perphénazine, haloperidol</td>
<td>Laersen et al. 2001</td>
</tr>
<tr>
<td>Woman in her fifth decade</td>
<td></td>
<td>Gaertner et al. 2001</td>
</tr>
<tr>
<td>Olanzapine 150-300mg/day</td>
<td>Fulminant hepatic failure</td>
<td>Albert Chang et al. 2008</td>
</tr>
<tr>
<td>34 years old men</td>
<td>Fatal acute fulminant liver failure</td>
<td>Macfarlane et al. 1998</td>
</tr>
<tr>
<td>Olanzapine 150-300mg/day</td>
<td>Acute hepatitis</td>
<td>Jang SJ et al. 1999</td>
</tr>
<tr>
<td>37 years old men</td>
<td>Hepatitis and eosinophilia</td>
<td>Raz et al. 2001</td>
</tr>
<tr>
<td>Olanzapine 10mg/day</td>
<td>Isolated asymptomatic increase in the aminotransferase levels</td>
<td>Cadario 2000</td>
</tr>
<tr>
<td>17 years old men</td>
<td>Cholestasis</td>
<td>SY Lui et al. 2009</td>
</tr>
<tr>
<td>Risperidone 6mg/day</td>
<td>Acute cholestatic hepatitis</td>
<td>Wright TM et al. 2007</td>
</tr>
<tr>
<td>30 year old men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone 2mg/day</td>
<td>Acute cholestatic hepatitis</td>
<td>Llinares et al. 2005</td>
</tr>
<tr>
<td>64 year old men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone: 2-6mg/day</td>
<td>Cholestatic hepatitis</td>
<td>Krebs et al. 2001</td>
</tr>
<tr>
<td>37 year old men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Acute cholestatic hepatitis</td>
<td>Wright TM et al. 2007</td>
</tr>
<tr>
<td>30 year old men</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

As far as liver disorders are concerned, it is important to make the difference between isolated biological disorders and disorders associated with clinical symptoms. It is also important to determine when the initiated treatment must be stopped.

When we compare different studies, it is proven that hepatitis on atypical neuroleptics is uncommon in comparison with asymptomatic biological disorders. The two terms are defined as follow: (Dumortier et al. 2002).

**Biological disorder:**
- increase of ASAT-ALAT (1.1 to 6 times the standard);
- increase of alkaline phosphatase (1.1 to 1.7 times the standard).

**Acute biological disorder:**
- if the increase is superior to values mentioned above;
- if the increase is associated with clinical symptoms.

This liver disorder can be cholestatic or cytolytic (Krebs et al. 2001). The asymptomatic increase of enzymes occurs usually during the first month after the treatment. This increase will be more frequent if one of the following risk factors is also present:
- age and sex (male);
- risk in relation to the daily dose and the plasma concentration;
- alcohol history;
- liver disease history (including Gilbert’s disease);
- obesity.

**Summary of liver disorder cases related to treatment with antipsychotics**

It seems that the increase of liver enzymes is rather more frequent with Clozapine and Olanzapine than with Risperidone or Quetiapine.
Very rarely, cases of jaundice (cytolitic and cholestatic) (between 0.1 to 0.01%) have been described and most of them were reversible when treatment stopped. Note that the fulminant hepatitis has a frequency inferior to 0.01% (Chang et al. 2009).

Discontinuation occurred in many cases. However, a decrease of the posology leads to a normalization of enzymes particularly in the cases of Risperidone and Clozapine. A switch to another molecule can provoke a decrease of liver enzymes. However, the switch to another neuroleptic can also generate an increase of liver enzymes.

Indeed, a recent study (Wright et al. 2007) showed that cholestasis can appear after years of treatment and appear again with a new antipsychotic agent.

Treatment discontinuation

It is important to consider the pros and cons of discontinuation. It is necessary to evaluate first the seriousness of the hepatic disorder and the possibility of a close clinical follow-up. The only contra-indication to antipsychotic treatment is clinical hepatitis.

CONCLUSION

Different studies show that a slight and asymptomatic increase of enzymes is common in the treatment with atypical antipsychotics.

Clinical consequences are more frequent with Clozapine and Olanzapine.

It seems that the increase of liver enzymes is slightly more frequent with Clozapine and Olanzapine in comparison with Risperidone and Quetiapine.

The mechanism of hepatotoxicity is not known yet, but it seems to be a mechanism that is dose-dependent.

Precautions should be taken for patients:
• with history of liver disease;
• when using other drugs with risk of liver toxicity (valproic acid, phenytoin).

If an increase in enzymes appears during treatment, several steps are to be taken:
• a follow-up of liver enzymes;
• a decrease in the posology;
• a discontinuation must be considered if there is no increase of enzymes higher than the above mentioned values or if clinical symptoms appear.

REFERENCES

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Correspondence:
Pauline Manceaux
Université Catholique de Louvain
5530 Yvoir, Belgium
E-mail: pmanceaux@hotmail.fr