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

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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 labatory 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 Haloperiol.*

Conclusion: *the different mechanisms of hepatotoxicity are unknown at present but it seems that the hypersensibility 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*

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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 labatory 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 labatory investigations

	03/07	11/08	12/08	03/09	7/09	13/01/10	25/01/10	27/01/10	03/02/10	10/02/10
ASAT		43	16	56		42	26	27	32	46
ALAT		1	16	92		85	40	32	46	84
GGT	122	244	26	254	244	268	170	144	164	269

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

	Asymptomatic increase in the aminotransferase levels.	Cytolitic hepatitis	Cholestatic hepatitis	Steatosis
Clozapine	27	11	4	
Olanzapine	15	6	3	1
Risperdal	12	7	4	4
Quétiapine	3	2	1	

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

Treatment		Liver diseas	Refrences
Olanzapine: 300mg/day	49 years old men	The patient experienced lethargy and anorexie, and fever, eosinophilia, leuco-cytosis and abnormal liver parameters	*Chaplin AC, Curley MA, Wanless IR. 2009 Luo D et al. 2007 Laersen et al. 2001*
	A retrospective revieuw of 7263 treatment courses	It seems that the increase of liver enzymes is slightly more frequent with Clozapine in comparison with pérazine, perphénazine, haloperidol	*Gaertner et al. 2001*
Olanzapine 150-300mg/day	Woman in her fifth decade	Fulminant hepatic failure	*Albert Chang et al. 2008*
		Fatal acute fulminant liver failure	*Macfarlane et al. 1998*
		Acute hepatitis	*Jang SJ et al. 1999*
Olanzapine 20mg/day	34 years old men	Hepatitis and eosinophilia	*Raz et al. 2001*
		Isolated asymptomatic increase in the aminotransferase levels	*Cadario 2000*
Olanzapine 10mg/day	17 years old men	Cholestasis	*SY Lui et al. 2009*
Risperidone 6mg/day	30 year old men	Acute cholestatic hepatitis	*Wright TM et al. 2007*
Risperidone 2mg/day	64 year old men	Acute cholestatic hepatitis	*Llinares et al. 2005*
Risperidone: 2-6mg/day	37 year old men	Cholestatic hepatitis	*Krebs et al. 2001*
Quétiapine	30 year old men	Acute cholestatic hepatitis	*Wright TM et al. 2007*

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 mentionned values or if clinical symptoms appear.

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