Asymptomatic inflammatory hepatopathy associated to use of Mirtazapine: Case Report.

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Mirtazapine is un atypical antidepressant with complex characteristics, including agonist/ antagonist activity in a wide variety of receptors causing therapeutic effects on anxiety, depression and sleep. However, cases of hepatical lesions induced by antidepressants with no symptomatology have been reported, under hepatocellular, cholestasic and mixed variations. This is the case of a patient who incidentally had changes in hepatical analysis after using Mirtazapine. Based on this a brief review of the evidence to date has been made.

Key words: *Mirtazapine, antidepressants, liver, asymptomatic (Source: BIREME)*

INTRODUCTION

The liver is our main biotransformation organ. It is particularly susceptible to toxicity related with oral medication, due to high concentration of medicines and their metabolites in the blood portal instead of the real objective area of the central nervous system. However, it is difficult to attribute hepatical damage to a specific medicine in clinical practice. Susceptibility of an individual to hepatical lesions induced by medicines depend on multiple genetic and epigenetic factors, such as age, sex, weight and consumption of alcohol that influence on appearance of hepatical adverse effects. Older patients seem to be more vulnerable; women have a stronger tendency to toxic hepatical reaction than men. Some ethnic differences have been reported as well. Some cases of hepatical lesion induced by use of antidepressants have been reported.[1][6]

Mirtazapine is an atypical antidepressant whose complex pharmacological characteristics include antagonist activity in subtypes of multiple receptors including noradrenalin (adrenergic α2), serotonin (5HT; 5HT2a, 5HT3) and histamine (H1), and inverted antagonist/ agonist activity in the 5HT2c receptor.[2] Given this wide range of interactions of the receptors, Mirtazapine has been widely used in clinical practice for treating depression and other symptoms, such as anorexia, lack of sleep and anxiety[3].

It is important to highlight that both serotonin and histamine clearly modulate immunity[3]. Besides, active receptors of Mirtazapine are expressed in macrophages/monocytes and may alter its function[3]. Therefore, it is possible that treatment with Mirtazapine may affect hepatical inmunity, with associated effects on systemic autoimmunity. According to this, it has been recently reported that treatment with Mirtazapine (only among all types of antidepressants) improves hepatical results and survival in patients with primary bile cholangitis with autoimmune hepatical disease[4][5]. However, other studies have described paradoxical results of low frequency

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of hepatical lesions when using Mirtazapine.

Next we shall see the case of a female patient who experienced asymptomatic hepatical alterations due to incidental use of Mirtazapine her hospitalization in a Mental Health Service of a General Hospital.

CASE REPORT

The patient is a 58-year-old woman. She is a housewife, single. living with her younger brother. She has full secondary education and is from Lima. She originally comes from the District, Villa el Salvador. She is Catholic. She was first hospitalized at the Mental Health Hospitalization Unit. at Hospital de emergencias, Villa el Salvador (HEVES) for 18 days, due to a suicidal ideation with deceiving clinical improvement after a few days. She was discharged with medication of Sertraline, 50 mg/day and Mirtazapine, 30 mg/day.

After this deceiving resolution of this current episode, one day after she was discharged, she was at home and started to feel anxiety, instability when walking, shivering, cephalea, difficulties to perform daily household chores, death ideation, isolation, difficulties to defecate, fatal ideas about her life, isolation, lack of appetite and did not follow her treatment. The next day she had the same symptoms, but worse, adding insomnia, continuous crying, motor unrest and suicidal ideation. One day later, she had increasing somatization, disability ideation, guilt. She asked her brother for "caustic soda, as she did not ant to keep living". That is why she was once again taken to the Emergency Room, at the same hospital. She was re admitted in the Mental Health Hospitalization Unit to the be evaluated by the Psychiatrist in charge.

The patient had a background of depressive episodes, hypothyroidism under treatment, a benign kidney tumor, allergy to sulfas and chronic gastritis.

When she was admitted some complementary blood tests and urine tests were made. The results of hemogram, glucose, urea, creatinine, lipidic/thyroid profile and full urine tests were within normal parameters. However, results of hepatical profile had some alterations, which led to continue studying these atypical findings.

Internal medicine evaluation decided to make a study in order to discard toxic, metabolic, infectious and pharmacological origin of the pathology. Complementary tests were requested, such as hepatitis profile (VHA, VHB, VHC), erythrocyte sedimentation rate (VSG), Lactate dehydrogenase (LDH), C reactive protein (PCR), Prothrombin time (TP), antimitochondrial antibody (AntiAMA), anti smooth muscle antibodies (Anti ASMA) and full abdominal ultrasound, whose findings were within normal parameters. On the other hand, results of hepatical profile increased their values that were already altered. No evidence of hepatical symptoms were found. In a second evaluation made by the Internal Medicine Dept it was recommended to suspend Sertraline and Mirtazapine, because of a possible Cytotoxic Hepatopathy. The following Table depicts values of hepatical profile associated to medicamentose dose (Table 1).

According to clinic evolution, the patient remains under study due to asymptomatic hepatopathy, handling of recurrent depression, hypothyroidism and somatizations for 54 days. Finally values of hepatical profile were reinstated, and the patient remained asymptomatic, and her affective state improved. During her stay psychotherapy cognitive behavioral in charge of psychology, and work therapy in charge of nursery personnel was implemented as well. She was discharged with medication of Sertraline, 25 mg/day, Clonazepam, 0.25 mg/day and levothyroxine, 50 mg/day.

DISCUSSION

Hepatical damage related with medicines is a significant health problem and occupies the fourth place between the causes of hepatical damage in western countries. That is the most frequent to eliminate medication from the market and reject trading requests in USA. IT is estimated that every seventh case of acute hepatic insufficiency is related with an adverse medicamentose reaction (RAM), and hepatical damage due to use of medicines has become the main cause of urgent hepatical transplant.[6]

After using medication, abnormal mild asymptomatic hepatical function in 0.5% to 21% of patients treated with second generation antidepressants is reported, as selected

Table N°1. Treatment Scheme during Hospitalization and Results of Hepatic Profile

Date	07-25-19	2/8/2019	6/8/2019	9/8/2019	08-13 -19	08-20 -19	08-27-19	5/9/2019
Medication								
Sertraline (mg/d)	100	100	100	Suspended	-	-	-	25
Clonazepam (mg/d)	1	0.75	0.75	0.75	0.5	0.5	0.5	0.5
Mirtazapine (mg/d)	30	30	30	Suspended	-	-	-	-
Levotiroxina (ug/d)	50	50	50	100	50	50	50	50
Hepatic Profile								
TGO	71	-	466	251	160	46	55	48
TGP	143	350	508	424	391	116	78	65
FA	108	-	186	207	202	169	150	122
GGTP	236	298	411	100	477	392	221	-

inhibitors of serotonin reuptake (ISRS) and inhibitors of serotonin-norepinefrin reuptake (IRSN) and till 3% of the patients treated with inhibitors of the monamine oxidase (MAO) or tricyclic and tetracyclic antidepressants. The incidence of hepatical damage is estimated in 4 out of 100,000 patients per year for tricyclic/ tetracyclic antidepressants. In general, incidence of hepatical toxicity induced by antidepressants requiring hospitalization is only 1.28 to 4 cases for 100,000 patients per year. No cases in Peru of hepatical complication associated to the use of antidepressants have been reported.[7]

in 2016, Gahr identified that use of Mirtazapine represented 1.5% of reported cases of severe hepatical events, according to the global perspective, but not specifying type of induced adverse effect.[6]

Billioti De Gage, in 2018 made a cohort study including 4,966.825 patients who started to use antidepressants identified in the data base of the French National Health Insurance. 382 severe hepatical lesions, in general were identified; however, the rate of standardized incidence per age and gender, every 100,000 people per year were 32.8 for Mirtazapine, so it was far from the risk correlation of severe hepatical lesion when compared with IRSS.[8]

It is well known that hepatical lesion pathology induced by medicines is divided into cholestasic, hepatocellular or mixed lesion, according to the particular abnormality detected in the hepatical function tests. The cholestasic lesion is featured by the direct damage to canalicular membranes and bile carriers, resulting in obstruction of the bile duct and increase of alkaline phosphatase (as define by an ALT/ALP of 2 correlation). On the other hand, hepatocellular lesion appears with high levels of ALT with little or no changes in ALP. The finding of higher levels of ALT than 2 times the upper normality limit or a ALT/ALP correlation of 5 or more is considered an acute hepatocellular lesion.[9]

In case of hepatical lesion induced by Mirtazapine, it is associated mainly with a cholestatic lesion, however, it has been associated to an asymptomatic increase of ALT enzymes in 2% of the cases.[10] Two case reports of 3 patients with hepatical damage induced by Mirtazapine have been published. According to the correlation criteria of ALT / FA, 2 of these cases were cholestatic hepatocellular mixed type[11]. The other was of cholestatic type[12]. In both, abnormalities of the hepatical enzymes values were normalized once the Mirtazapine was removed from the therapeutic medications.

This hepatical phenomenon happened in our patient, as the values of transamines TGO, TGP, FA and GGTP quickly increased within a few

days while the combination between Sertraline and Mirtazapine remained the same. The lesion was assumed to be mixed, despite no findings in the full abdominal ultrasound tests and no symptomatology appeared. The most adequate decision was to suspend both antidepressants after discarding infectious, metabolic and toxic cause. After reviewing the therapeutic background, the patient had received Sertraline in the same dosage for treatment of prior depressive episodes, so later it was decided to reuse such medication in moderate dosage. After suspending Mirtazapine restoration of the values of transaminases and FA with no symptomatology was observed.

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