Annals of Clinical Case Reports

Case Report
Published: 09 Jun, 2017

Neuroleptic Malignant Syndrome without Hyperthermia Induced by Aripiprazole Extended-Release Injection

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Abstract

Neuroleptic malignant syndrome may be considered an idiosyncratic neurological condition with potentially lethal consequences associated with the assumption of all antipsychotics, first described in the early sixties in association with the antipsychotic haloperidol. Recently, several cases of the syndrome have been reported in literature as a complication of typical and atypical antipsychotic drugs. Moreover, a widespread use of antipsychotics in numerous neuropsychiatric disorders has lead to the analysis of the risks and consequences of neuroleptic malignant syndromes. This case report describes the occurrence of a neuroleptic malignant syndrome in a 55-year-old woman with intellectual disability presenting with organic delusional disorder, following administration of aripiprazole extended-release injection. Although cases of neuroleptic malignant syndrome induced by aripiprazole or by atypical antipsychotics extended-release have been published in literature, this is the first case report regarding a neuroleptic malignant syndrome induced by aripiprazole extended-release injection.

Keywords: Neuroleptic malignant syndrome (NMS); Aripiprazole extended-release injection; Antipsychotic drugs

Introduction

Neuroleptic Malignant Syndrome (NMS) is a rare, idiosyncratic and unpredictable adverse reaction associated to antipsychotic use with life-threatening [1] consequences. All antipsychotics may be associated with the development of a neuroleptic malignant syndrome, especially the first generation antipsychotics (Table 1). The incidence rate of NMS in subjects treated with antipsychotic drugs is actually approximately 0.02%, compared to a rate of 3% recorded 50 years ago [2]. The syndrome occurs in all age groups (including children), but young adults are more affected [3], and the male/female ratio is 2:1 with a high mortality rate in 10-20% of cases. However, lower mortality rates have recently been observed most probably related to early detection of NMS and improved management [2]. The key risk factors for neuroleptic malignant syndrome are demographic (male gender), environmental (restraint, dehydration) and pharmacological (polypharmacy, oral haloperidol, aripiprazole, long-acting flupentixol), because of their pharmacodynamics mechanism. Concurrent medical conditions are also relevant (delirium, confusion) [4]. Authors reported a correlation between a higher proportion of antipsychotics, the pharmacokinetic properties and the severity of the syndrome [5].

The pathogenesis is still unknown [1], but investigations have revealed involvement of two main mechanisms: an abnormal reaction of skeletal muscle with a central D2 receptor blockade [6] and the removal of tonic inhibition from the sympathetic nervous system, with sympathoadrenal hyperactivity and dysfunction leading to autonomic dysfunction [7]. The clinical features are often heterogeneous in onset, presentation and progression. Most patients develop mental status change with delusion, mutism and catatonia, then muscular lead pipe rigidity with tremor, hyperthermia (above 38°C) and autonomic instability [1,8]. Leukocytosis and Creatine Kinase (CK) elevation are commonly observed. The largest systematic review of literature comparing the characteristics and differences of the neuroleptic malignant syndrome induced by first and second generation antipsychotic has reported a lower incidence and severity of symptoms with second-generation antipsychotics with fewer extrapyramidal symptoms and less rigidity [8].

In neuroleptic malignant syndrome subsequent to administration of aripiprazole, rigidity and autonomic symptoms are present in all cases reported [9], with a lower frequency of hyperthermia, diaphoresis and tachypnea than in neuroleptic malignant syndromes induced by other second-generation antipsychotics [1]. However, literature reports three cases of neuroleptic malignant

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Received Date: *08 May 2017*
Accepted Date: *01 Jun 2017*
Published Date: *09 Jun 2017*

Citation:
Ilario C, Sentissi O, Coste C. Neuroleptic Malignant Syndrome without Hyperthermia Induced by Aripiprazole Extended-Release Injection. Ann Clin Case Rep. 2017; 2: 1372.

ISSN: 2474-1655

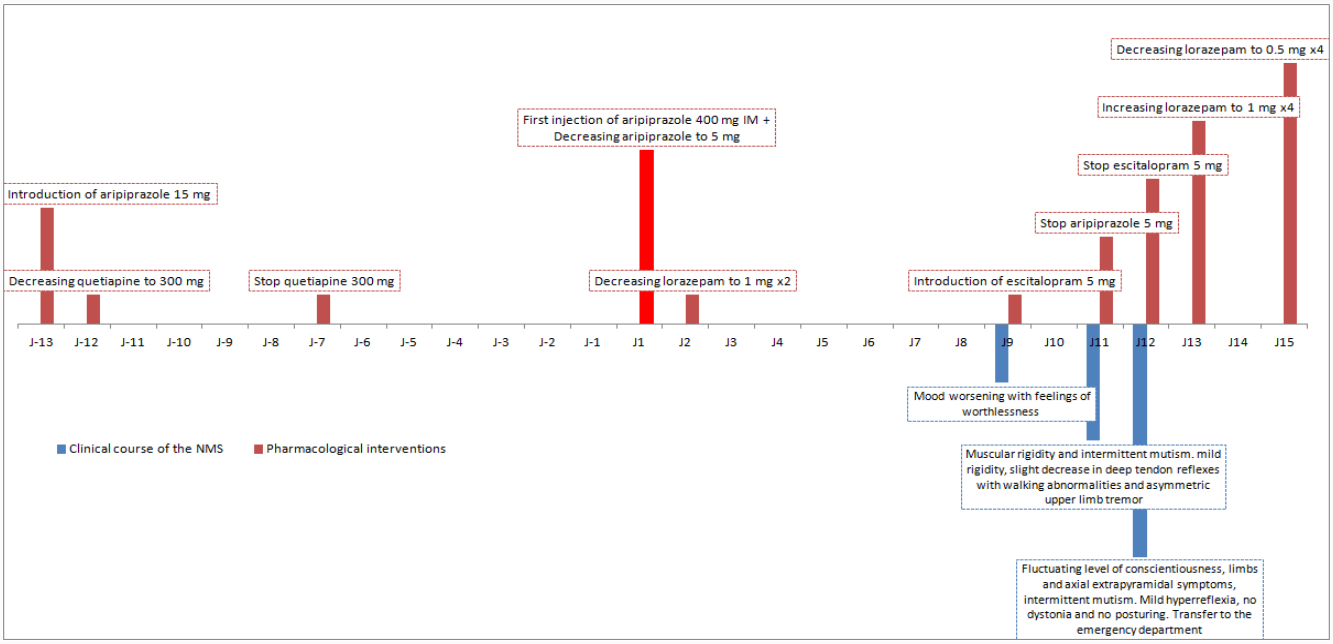

Figure 1: Course of symptoms in our case and pharmaceutical interventions.

syndrome induced by aripiprazole in which pyrexia was absent [10-12]. On average, neuroleptic malignant syndrome develops 14 days following the initial administration of aripiprazole with a mean prescribed dosage of 5 to 30 mg/day [9], in some clinical illustrations, in association with other psychotropic drugs, such as selective serotonin reuptake inhibitors (fluoxetine and escitalopram) [9]. Selective serotonin reuptake inhibitors (SSRIs) may contribute to the development of neuroleptic malignant syndrome with an increase in serotonin which inhibits dopamine release in the ventral tegmentum area and the substantia nigra [13] and thereby may worsen a hypodopaminergic state induced by antipsychotics. NMS has been reported also in association with escitalopram and citalopram, antidepressants that are not known to inhibit the cytochrome P450 system (the Cyt P450 system is not relevant for NMS-development) [13,14]. Twenty-nine cases of neuroleptic malignant syndrome in association with a second-generation antipsychotic and serotonergic antidepressants have been published in literature, but only one case involved oral aripripazole and escitalopram, with symptoms appearing after one week of treatment [13,15]. The different types and presentations of NMS could be explained by: different risk factors in populations; possible association of NMS with other lethal syndromes; incidence of NMS in patients treated by neuroleptic agents, which is still unclear (from 0.7% to 2.2%) [6].

In our knowledge, this is the first case report concerning a neuroleptic malignant syndrome induced by aripiprazole extended-release injection, medication, which is increasingly being prescribed by clinicians.

Case Presentation

Mrs F, a 55-year-old Caucasian single woman presented a medical history of intellectual disability caused by traumatic brain injury at the age of 17, and organic delusional disorder with supposedly related temporal lobe epilepsy**.** She was monitored in outpatient psychiatric basis and received treatment with quetiapine 300 mg twice daily, lorazepam 1 mg three times daily and amlodipine 5 mg daily. However, the patient experienced an episode of aggressiveness consistent with delusional phenomena and recurrences due to poor treatment compliance. She was admitted to our psychiatric crisis unit for the fourth time in 2016, accompanied by her mother following an acute exacerbation of auto and hetero-aggressiveness and delirious speech. In a patient with organic encephalopathy, using atypical antipsychotics is "off-label", but in this clinical situation of chronic psychosis and behaviour disorder such as aggressiveness, this treatment remains one of the few options available. On admission, Mrs F presented an abrupt change from baseline mental status with severe anxiety and inappropriate affect. On examination, no abnormalities were detected. Urine and blood tests were within normal limits. Following consultation with the patient and her family, we decided to switch to aripiprazole extended-release injection (400 mg), in favour of its adequate safety profile, few metabolic side effects and its powerful/ solid anti-impulsive and antipsychotic effects. Subsequently, we prescribed oral aripiprazole 15 mg/day with a reduction of quetiapine at 300 mg/day for a week, then discontinued. The first injection of aripiprazole extended-release (400 mg) was administered fourteen days after oral administration (Figure 1). No side effects were observed. The level of aripripazole the day after the injection was at 507 nmol/l (330-1115 nmol/l), and active metabolite (dehydroaripiprazole) at 287 nmol/l. Ten days after the treatment, the level of aripiprazole was at 332 nmol/l and the level of dehydroaripiprazole at 225 nmol/l. Eight day after the injection, the patient experienced mood worsening with feelings of worthlessness and escitalopram 5 mg/day was introduced. Eleven days after the first injection of aripiprazole extended-release, the patient complained of muscular rigidity and intermittent mutism. The examination showed a mild rigidity, slight decrease in deep tendon reflexes with walking abnormalities and asymmetric upper limb tremor. The hematologic parameters and ionogram were within normal limits. The day after, the patient was transferred to the emergency department with suspected neuroleptic malignant syndrome due to a sudden deterioration of the clinical symptoms (dilated pupils, heavy sweating and diarrhea were absent). The patient was aggressive and presented fluctuating level of conscientiousness, limbs and axial extrapyramidal symptoms (such

Table 1: Neuroleptic malignant syndrome induced by aripiprazole.

Article	Cases	Indication of aripiprazole treatment	Dosage of aripiprazole	Day to onset	Symptoms	Main findings	Duration of NMS
Trollor [9]	Nine cases	Psychotic disorder (67%) Affective disorder (22%) Other (11%)	Mean 18 mg/day Range 5-30 mg/day	Range 2-270 days	Rigidity (100%), altered mental status (78%), hyperthermia range 37.1-38.4°C (78%)	Men (67%), age lower than typically seen in NMS, CK>1,000 U/L (50%), white cell count elevated (75%)	Unknown
Belvederi [1]	Five more cases	Psychotic disorder (71.4%) Affective disorder (21.4%) Other (7.1%)	Mean 18.9 mg/day	Earlier or on the same day of NMS diagnosis	Rigidity (100%), altered mental status (100%), lower frequency of hyperpyrexia, nausea and vomiting	Rhabdomyolysis associated with a lower peaks of CK	Mean 7.5 days
Molina [10]; Chakraborty [11]; Spalding [12]	Three cases without fever	paranoid schizophrenia childhood-onset schizophrenia paranoid schizophrenia	15 mg/day 30 mg/day 15 mg/day	270 days 2 days 3 days	Rigidity, choreoathetoid movements Rigidity, mutism Rigidity, mutism, catatonia	CK:103 U/L CK:955 U/L CK:762 U/L	9 days 7 days unknown, more than 4 days
Our case report	One case	organic delusional disorder	Aripiprazole extended-release 400 mg IM	Eleven days	Muscular rigidity, asymmetric upper limb tremor and akinetic mutism	Leucocytosis CK: 8,.511 IU/L	60 days

as severe rigidity, hypokinesia, dysphagia and asymmetric upper limb tremor), poverty of speech, intermittent mutism. Mild hyperreflexia, no dystonia and no posturing. Mrs F's temperature was 37.5°C, blood pressure 155/93 mmHg, pulse 106 beats per minute, respiratory rate 20 per minute (baseline for the subject: 140/80 mmHg, 70 beats per minute). Laboratory data showed leukocytosis (13,000 cells/mm^3), increased creatine phosphokinase (CK: 8,511 IU/L) and acute renal failure (serum creatinine: 89 µmol/L; glomerular filtration flow: 63 mL/min/1.73m^2), other blood test values, complete metabolic panel and ionogram levels were all within normal limits. Immediate electroencephalographic (EEG) examination showed global slow activity without argument for comitiality or metabolic disorder. The magnetic resonance imaging showed damage to the left temporal lobe caused by brain injury (at the age of 17).

On Sachdev rating scale for NMS [16], Mrs F's rating is 16 on 36. When NMS is suspected, a score superior to 8 is in favour of the diagnosis. On Naranjo Scale, Mrs F's rating is 9 on 13, a score superior to 9 is in favour of the diagnosis of adverse drug reaction.

Some drugs, like bromocriptine mesylate (a dopamine agonist), could be used to treat NMS. However, the supportive and symptomatic therapy is the most common treatment, because the safety of other therapies is still unclear. So, the supportive treatement was started. Oral aripiprazole and escitalopram were discontinued abruptly (the most important intervention), lorazepam 0.5 mg 4 times a day was administred with nursing care, close clinical and paraclinical monitoring. The patient overall showed slow but progressive improvement in motor and cognitive functions. However, during the two months of treatment in a somatic unit, she developed a number of complications: acute renal failure due to rhabdomyolysis for which a intravenous hydratation has been helpful; acute urinary retention that required the instalment of a probe; acute aspiration pneumonia due to swallowing impairment, treated with clindamycin (injection 600 mg 1x/8h, 1800 mg daily). The patient recovered gradually and benefit from progressive administration of clozapine, before returning to our unit. After four months of inpatient care, Mrs F finally went back home.

Discussion

We report a case of a patient with neuroleptic malignant syndrome induced by Aripiprazole Extended-Release Injection. We carried out an exhaustive literature review and we found eighteen published case reports with similar characteristics following administration of aripiprazole [1,9-12] (Table 1), not related to an "off-label" use.

In this clinical situation, rigidity and autonomic characteristics were observed, in line with all cases of neuroleptic malignant syndrome caused by aripiprazole reported. These symptoms are more common compared to cases of patients using clozapine, olanzapine and quetiapine [9]. Furthermore, other extrapyramidal signs detected in our patient such as tremor and hypokinesia, are predominantly related to aripiprazole compared to both traditional [17] and atypical antipsychotic drugs [9].

The atypical clinical presentation of NMS following aripiprazole administration could be related to its peculiar pharmacodynamic profile [1]. In fact, aripiprazole possesses a partial agonist activity at D2 and 5-HT1A receptors and antagonistic activity at 5-HT2A receptors, with an affinity 20-fold lower than haloperidol affinity for D2 [10]. This unique characteristic may be related to the lower severity rate and duration in contrast to neuroleptic malignant syndrome induced by other atypical antipsychotics.

Neuroleptic malignant syndrome may be deceptive in presentation. The most important differential diagnosis is serotonin syndrome, which can have similitudes in clinical presentation [2]. Hyperthermia, tremor and alteration of mental status can occur in both, but muscular rigidity, hypertonia and bradykinesia are specific in NMS. Moreover, symptoms are progressive in NMS whereas in serotonin syndrome they develop faster. In some cases an overlap of neuroleptic malignant syndrome and serotonin syndrome may occur [18].

In this case, the progressive installation of extrapyramidal symptoms (tremor, hypokinesia and severe rigidity), mutism and dysphagia associated with CPK elevation and leucocytosis is in favour of a NMS. However in our case report a typical feature of serotonin

syndrome, hyperreflexia, was present on diagnosis, most likely related to the use of therapeutic doses of escitalopram.

Neuroleptic malignant syndrome is a life-threatening neurologic emergency, and the risk of a recurrent episode after restarting on neuroleptic agents is relatively high but difficult to quantify. An apparent decrease in severity is, however, suggested by the lower mortality rate reported in the last decade [10]. This may relate to early detection of neuroleptic malignant syndrome as well as to improvements in management of the condition or lower severity with atypical antipsychotics [6]. Subsequent to neuroleptic malignant syndrome, over 30% of patients develop major complications during the first weeks, together with potential persistent long-term sequelae [19]. Considering the impact of genetic polymorphisms on the elimination of aripiprazole, a genotype / phenotype test of CYP2D6 may also be proposed. Allelic variants altering CYP2D6-mediated metabolism may be associated with an increased risk of NMS [13].

Case reports of neuroleptic malignant syndrome induced by aripiprazole or by second-generation antipsychotics extended-release have been published in literature, but we report herein the first case of a neuroleptic malignant syndrome induced by a different formulation of aripiprazole, the extended-release injection never been described in the literature. In conclusion, this original case report may be considered important contribution for clinicians in their daily practice in order to appropriately investigate and address to the serious side effects of extended-release injection of aripiprazole, causing a more prolonged course of NMS. The atypical clinical presentation of NMS following aripiprazole administration could be related to its peculiar pharmacodynamic profile, which represents a modern and innovative therapeutic tool in the treatment of major psychiatric disorders [20]. However, this case report cannot give information on incidences or prevalence and further research is required to increase our knowledge of the consequences and efficacy of treatments and to better understand neuroleptic malignant syndrome, especially in the extended release formulation.

Acknowledgments

We would like to thank Mrs Giuseppina Caraglia for the English editing.

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