Aripiprazole and neuroleptic malignant syndrome

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Aripiprazole, an atypical antipsychotic with a novel method of action, has only recently been awarded a license in the UK. We report our first patient to receive this drug, who had treatment-resistant schizophrenia and developed neuroleptic malignant syndrome (NMS) with aripiprazole. To our knowledge, this is the first published case report involving aripiprazole and NMS in a potentially fatal medical emergency. Further experience with this drug should indicate whether this is an isolated case (as described with other atypical antipsychotics) or constitutes a more serious risk than that suggested by the relatively beneficial therapeutic profile described in the literature to date. ***Int Clin Psychopharmacol*** **19:351–353 © 2004 Lippincott Williams & Wilkins.**

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Conflict of interest: Dr Johnston has previously received educational sponsorship from numerous companies who market atypical antipsychotic drugs that are licensed in the UK. This includes a sponsorship from Otsuka/Bristol Myers Squib (the company that markets Aripiprazole) to attend a European Conference in 2003.

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Introduction

Atypical antipsychotic drugs represent a landmark in the treatment of schizophrenia and schizoaffective disorders. To be classified as an atypical antipsychotic, a drug should prove its efficacy against both the positive and negative symptoms of schizophrenia; it should be outstandingly efficient in patients with partial response or non response to typical antipsychotics; and have at least two of the following characteristics: no association with subjective dysphoria, low sedative effects, few cardiac autonomic effects, mild elevation of prolactin, lower sexual dysfunction and minimal weight gain. Atypical antipsychotics must also show their efficacy in the treatment of depressive symptoms and cognitive deficits of schizophrenia (Garcia-Anaya *et al.*, 2001). Nevertheless, cardiovascular side-effects, neuroleptic malignant syndrome (NMS), weight gain, hyperprolactinaemia, diabetes and hyperlipidemia have all been reported with atypical antipsychotics.

Aripiprazole, marketed as 'Abilify', is the latest atypical antipsychotic to come into clinical practice. It has been very recently licensed in the UK, in contrast to the USA, where it has been available for several years. It has a proposed mechanism of action, which is novel in comparison to other atypical antipsychotic agents. Aripiprazole is a dopamine D_2 receptor partial agonist with partial agonist activity at serotonin 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors. This particular pharmacological feature characterizes a new class of atypical antipsychotics that does not match the original concept of a therapeutic occupancy window for atypical antipsychotics. Hence, aripiprazole has also been referred to as a 'third generation' antipsychotic. Aripiprazole, of which the antipsychotic efficacy has been proven in various multicentre clinical trials, leads to almost complete saturation of D_2-like dopamine receptors at clinically used doses; however, the incidence of extrapyramidal side-effects with aripiprazole is no higher than with placebo. The most likely explanation for this finding is aripiprazole's weak partial agonism at D_2-like dopamine receptors (Buckley, 2003; Grunder *et al.*, 2003; Keek and McElroy, 2003).

Placebo-controlled comparative trials of aripiprazole confirm its efficacy for positive, negative symptoms of schizophrenia and general psychopathology (Kane *et al.*, 2003; Buckley, 2003; Potkin *et al.*, 2003; Taylor, 2003). Treatment-emergent adverse effects appear low. Aripiprazole does not appear to cause significant extrapyramidal side-effects, hyperprolactinaemia, excessive weight gain (Buckley, 2003) or cardiac rhythm disturbance (Keek and McElroy, 2003). Limited data suggest that aripiprazole is not associated with impaired glucose tolerance (Taylor, 2003). Short-term clinical trials demonstrated efficacy in acute exacerbations, and long-term studies showed that aripiprazole could maintain remission of schizophrenia. Most adverse events were mild. The incidence of extrapyramidal symptoms was low, with akathisia being the most common (Bowles and Levin, 2003).

Aripiprazole, being a relatively new drug, is still under study. There is a dearth of literature reporting serious

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side-effects with this medication. Here, we report a case of neuroleptic-induced neuroleptic malignant syndrome with aripiprazole.

Case report

The patient was a 42-year-old Caucasian male, known to the local psychiatric services since the age of 14 years. He was diagnosed with childhood schizophrenia.

Throughout the course of his illness, he was put on various antipsychotics, both typical and atypical. He did well for a number of years on Fluphenazine depot, which was eventually stopped due to emerging tardive dyskinesia. With clozapine, he demonstrated some therapeutic benefit initially, but his family was concerned about their son's impaired concentration while on clozapine, and were apprehensive about increasing its dose beyond 300 mg per day. He showed significant deterioration on quetiapine. He became more and more withdrawn and hallucinated quite frequently. His tardive dyskinesia re-emerged and was getting worse on the quetiapine. He was on 350 mg of quetiapine when he was hospitalized this time, with a view to revise his medication.

The patient was admitted with a significant deterioration in his mental state. He was actively hallucinating, and very withdrawn in his behaviour. Due to a lack of appropriate response to other antipsychotics, a decision was taken to start him on aripiprazole. Aripiprazole was first started at the dose of 15 mg nocte and then increased to 30 mg nocte after 1 week. During this period, his condition remained much the same, without much improvement or deterioration.

Within 2 days of increasing the dose of aripiprazole, he started getting markedly more withdrawn. He became mute and stopped eating and drinking on his own. He would sit in the same position for hours. It took much persuasion and prompting to make him walk to the dinner table and eat his meals. He had marked muscle rigidity. On investigation, his creatinine kinase was first raised to 271 U/l. Within another 24 h, it had risen to 955 U/l. There was no history of trauma or intramuscular injections. He was also dehydrated and tachycardic. There was no pyrexia or autonomic instability.

The patient was diagnosed as having a neuroleptic-induced catatonia. There was concern due to his rising creatinine kinase and the onset of a NMS was considered as a differential diagnosis at this point. The aripiprazole was stopped and he was started on Lorazepam alone (1–2 mg p.r.n.). He was also transferred to the medical ward.

On the medical ward, he made an uneventful recovery with the benefit of supportive measures (intravenous fluids and nursing care). On stopping aripiprazole, his creatinine kinase started to fall gradually. It ultimately reached baseline in 8 days.

The patient was then transferred back to the psychiatric ward after 1 week. After discussion with his family, it was agreed that clozapine would be reinstated.

Discussion

This case is interesting in a number of aspects. The work of a number of investigators supports the concept of NIC-NMS (neuroleptic-induced catatonia-neuroleptic malignant syndrome) as a single spectrum disorder, which may present with varying degrees of severity (Hynes and Vickar, 1996; Fink, 1996; Fink, 2001). The diagnostic criteria for NMS comprise a controversial area among investigators, who differ among themselves about what should be considered to be the cardinal features of NMS. In a patient who shows full blown manifestation of all the symptoms of NMS, diagnosis is relatively easy. However, if the symptoms are few and relatively mild, considerable debate may ensue (Pelonero *et al.*, 1998). There is still no consensus regarding the diagnosis, pathophysiology and treatment of this potentially lethal medical condition (Gurrera, 2002).

All antipsychotics have been reported in the literature as being capable of inducing neuroleptic malignant syndrome, including rare reports of clozapine, olanzapine and risperidone-induced NMS (Caroff *et al.*, 2000). To our knowledge, there are no published literature regarding aripiprazole and NMS or aripiprazole and catatonia.

It was clearly evident that our patient had neuroleptic-induced catatonia. We also believe that his clinical picture was in keeping with mild to moderate NMS (according to the scoring system suggested by Hynes *et al.*, 1996). For NIC-NMS spectrum, our patient would have scored 5, supporting the evidence for a mild to moderate (NMS), which may have progressed to a more severe and full-blown picture if the aripiprazole had not been stopped timely. It is true that our patient did not develop pyrexia, but Hynes *et al.* (1996) have already reported a case of NMS without pyrexia in a 12-year-old boy. It has also been suggested that atypical antipsychotics may produce an atypical or milder form of NMS. There are case reports to suggest that extreme hyperthermia and extrapyramidal dysfunction are less frequent in NMS associated with atypical antipsychotics compared to the conventional ones (Caroff *et al.*, 2000).

There have been a number of comparative studies of aripiprazole with respect to the efficacy and tolerability profiles of other atypical antipsychotic medications, but more are warranted. Aripiprazole's clinical role will be

determined by further clinical experience and additional phase IV studies (Buckley, 2003).

Finally, although this case report illustrates the role of aripiprazole in inducing NMS, in the UK, it is clearly too early to conclude whether aripiprazole is more or less likely to produce NMS than other atypical antipsychotics. Ultimately, its unique pharmacological action may affect the cortical or subcortical pathways hypothesized to underlie NMS and alter the incidence of NMS in patients on aripiprazole compared to other atypical drugs. Aripiprazole's unique action is well accepted but whether it represents a further landmark in antipsychotic development remains an open question.

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