Brain Injury, January 2008; 22(1): 99–102

informa
healthcare

CASE STUDY

Aripiprazole is associated with early onset of Tardive Dyskinesia like presentation in a patient with ABI and psychosis

SYED HABIB HAIDER ZAIDI & RAFEY A. FARUQUI

Kemsley, National Centre for Brain Injury Rehabilitation, St Andrew's HealthCare, Northampton, UK

(Received 22 August 2007; accepted 21 November 2007)

Abstract
Purpose: This report describes the early onset Tardive Dyskinesia like presentation during treatment with Aripiprazole.
Case study: The patient, who had a history of acquired brain injury, was receiving treatment for his psychotic illness characterized by persecutory delusions, second person auditory hallucinations, self-neglect and challenging behaviours. Tardive Dyskinesia is not a well reported side-effect of Aripiprazole.
Conclusions: This report demonstrates onset of this side-effect upon commencement of Aripiprazole and cessation of this side-effect upon termination of this medication. This case report highlights the need for careful monitoring of neurological side-effects in patients with acquired brain injury requiring treatment with anti-psychotic medication.

Keywords: *Aripiprazole, side-effects, Tardive Dyskinesia, acquired brain injury (ABI), treatment of psychosis*

Introduction

Drug-induced neurological side-effects such as Dyskinesia, Dystonia and Akathisia are known to be associated with the use of psychotropic medications. Dyskinesia is the impairment of voluntary motor activity by superimposed involuntary motor activity [1]. Tardive Dyskinesia is defined as continuous slow writhing movements (i.e. athetosis) and sudden involuntary movements typically of the oral lingual region (Chorea) [1]. However, it can involve other parts of the body such as limbs and respiratory muscles. Tardive Dyskinesia (TD) can be debilitating and in many cases persistent [2, 3]. Akathisia can be described as an unpleasant feeling of motor and mental restlessness with a need to move, leading to an inability to keep still. This side-effect is associated with aggression, agitated behaviour and suicidal ideation [3].

Risk of developing Tardive Dyskinesia (TD) is an important concern in the long-term use of anti-psychotic (neuroleptic) medication [4]. The risk of persistent TD is reported to be 32% after 5 years of neuroleptic exposure, 57% after 15 years of exposure and 68% after 25 years of exposure [5]. Another study reports that the incidence of TD in young adults is 5% at 1 year, 10% at 2 years and 15% at 3 years [6]. Although atypical anti-psychotics are less likely to induce TD, several cases of emerging TD have been reported in patients treated with atypical anti-psychotic drugs [7].

This report describes the early onset and course of TD-like presentation emerging within 15 days of starting Aripiprazole (second generation anti-psychotic) in a patient with acquired brain injury (ABI), psychosis and mild learning disability. It used three well known and widely used neurological side-effects rating scales, BARS (Barns Akathisia Rating Scale) [8], Simpson Angus scale for Extra pyramidal side-effects (EPSE) [9] and AIMS (Abnormal Involuntary Movements Scale) [10] to assess the

Correspondence: Syed Habib Haider Zaidi, Senior House Officer, Kemsley, National Centre for Brain Injury Rehabilitation, St Andrew's HealthCare, Northampton, NN1 5DG, UK. Tel: 00 44 1604 616499. Fax: 00 44 1604 626249. E-mail: shaider@standrew.co.uk

ISSN 0269–9052 print/ISSN 1362–301X online
DOI: 10.1080/02699050701822493

nature and severity of neurological side-effects appearing during the course of treatment. The main advantage of these rating scales is that they provide a comprehensive rating of abnormal involuntary movements in various body sites; and are useful in monitoring the progress [11–13]. The clinical history and presentation of the patient fulfilled the Scholar and Kane RD-TD criteria (Research-Diagnosis for Tardive Dyskinesia) [14]. A brief description of above mentioned rating scales and RD-TD criteria is provided.

Side-effects rating scales and RD-TD criteria

- The Barnes Akathisia Rating Scale [8] is a four-item scale to assess the presence and severity of drug induced akathisia. It is the most widely used comprehensive rating scale for akathisia, including both objective items (e.g. observed restlessness) and subjective items (e.g. patient's awareness of restlessness and related distress), together with a global clinical assessment of akathisia. Global assessment is made on a scale of 0–5 with comprehensive definitions provided for each anchor point on scale: 0 = absent; 1 = questionable; 2 = mild akathisia; 3 = moderate akathisia; 4 = marked akathisia; 5 = severe akathisia.
- The Simpson-Angus scale [9] was devised to measure drug-induced Parkinsonism, providing standardized ratings for rigidity, tremor and salivation. The scale is entirely sign led. It contains 10 items, each rated on a 5-point scale (0–4), with descriptive anchors for each point and a clearly described examination procedure for each item. It is one of the most commonly used rating scale for drug-induced Parkinsonism in clinical trials over the past 25 years.
- AIMS [10] is a 12-items instrument assessing abnormal movements associated with anti-psychotic drugs, such as tardive dyskinesia and chronic akathisia as well as 'spontaneous' motor disturbances related to the illness itself. Scoring the AIMS consists of rating the severity of movements in three main anatomic areas (facial/oral, extremities and trunk), based on a five-point scale (0 = none, 4 = severe). Three separate items score global severity, the subject's awareness, and incapacitation due to involuntary movements (each on a 5-point scale). Two additional items cover the subject's dental status, as movements in the orofacial area are more obvious in edentulous patients.

Schooler and Kane [14] developed the research diagnosis for TD (RD-TD) for classifying TD type. The three pre-requisites of the diagnosis are as follows:

(1) A history of at least 3 months' total cumulative neuroleptic exposure. Exposure may be continuous or discontinuous.
(2) The presence of at least 'moderate' abnormal, involuntary movements in one or more body areas or at least 'mild' movements in two or more body areas (face, lips, jaw, tongue, upper extremities, lower extremities, trunk).
(3) Absence of other conditions that might produce abnormal involuntary movements.

Case report

A 25 year old single male presented to Brain Injury Rehabilitation services for assessment and management of his challenging behaviour and rehabilitation needs.

An inpatient assessment identified that, in addition to mild cognitive and communication difficulties, he was also suffering from a psychotic illness characterized by persecutory delusions, second person auditory hallucinations, self-neglect and challenging behaviours. He was initially treated with Risperidone along with occasional use of Chlorpromazine on an 'as required' basis. His Risperidone was gradually withdrawn, due to partial response on this medication. At this stage he had received more than 3 months of cumulative neuroleptic exposure. Risperidone was replaced by Aripiprazole. The involuntary movements were first noticed on day 15 of commencing Aripiprazole. At that time, the occasional 'as required' use of Chlorpromazine was terminated to further evaluate his condition.

The patient was periodically assessed using standardized clinical and side-effects scales, including the BARS (Barns Akathisia Rating Scale) [8], Simpson Angus scale (For EPSE) [9] and AIMS (Abnormal Involuntary Movements Scale) [10].The dyskinetic movements involved a moderate degree of perioral movements, including twisting and protruding movements of the tongue, sucking and lateral jaw movements. In addition to his dyskinesia, he also presented with features of akathisia. Aripiprazole was stopped on day 26 of commencing this medication, due to continued involuntary movements and observed and reported motor and mental restlessness. His akathisia subsided completely on day 32, 6 days after stopping Aripiprazole. The severity of dyskinetic movements also reduced gradually but dyskinesia was still present on this review. No other extra pyramidal side-effects were present during the examination. The jaw movements disappeared on

Table I. Incidence of TD on typical or second generation anti-psychotic medication.

Drugs	Incidence
Haloperidol (197 patients on 20 mg/day)	(4.6%) 203 days trial
Olanzapine (707 patients on 20 mg/day)	(1.0%) 237 days trial
Risperidone (503 patients)	(0.3%) 1 year trial
Clozapine (28 patients)	Very rare (two cases) 1 year trial
Quetiapine (184 elderly patients)	(2.7%) 1 year trial

Sources: Table has been developed using data from following sources. Llorca et al. (7) and Jeste, D.V. et al. (20).

day 35. Other oral-facial movements had decreased in intensity but were still clearly observable at this stage. Dyskinetic movements subsided completely on day 67.

The patient was commenced on oral Quetiapine soon after stopping aripiprazole. The dosage of quetiapine was titrated according to the clinical response. There was no evidence of any association or exacerbation of dyskinesia or akathisia with use of Quetiapine.

Discussion

There was a recorded TD prevalence of 5% in patients with schizophrenia before the introduction of anti-psychotic medication, rising to up to 20% or more thereafter. All patients treated with anti-psychotics are at risk of developing TD, although patients with affective illness, organic pathology such as diabetes and learning disabilities, female gender and elderly seem to be more likely to be affected [15]. Numerous studies have been conducted to determine the incidence or prevalence of TD in persons exposed to typical or second generation anti-psychotic medication. However, methodological differences including the use of different case definitions, variable patient groups, use of structured or unstructured ratings and time intervals between ratings make it difficult to compare results.

To the authors' knowledge, this is the first case report in which early onset tardive dyskinesia has been described in a patient treated with Aripiprazole. This case reports establishes a temporal relationship between commencing Aripiprazole and onset of TD in this patient. There was no evidence of presence of this side-effect prior to commencement of Aripiprazole. The side-effect persisted despite stopping the occasional low dose use of chlorpromazine. There was clear evidence that the side-effect was getting worse and becoming more prominent when Aripiprazole was continued at the dose of 15 mg daily.

Aripiprazole was stopped completely 11 days after the onset of TD and akathisia. Akathisia responded quickly to stopping this medication and gradually disappeared over the next few days, subsiding completely on day 6 of stopping Aripiprazole. It can be argued that this was indicative of a possible dose–response relationship and, as the bioavailability of the medication reduced, the side-effect intensity also reduced. Tardive Dyskinesia gradually reduced in intensity and continued for a total of 41 days after the medication was stopped completely. Introduction of another atypical anti-psychotic medication, Quetiapine, did not appear to have influenced the features or course of dyskinesia. Aripiprazole and Quetiapine have a relatively different receptor binding profile and this difference in receptor binding may have influenced the emergence of TD on one medication but not on the other one. The presence of EPSEs during treatment with anti-psychotics is associated with a 3-fold increase in risk of TD and it is likely that the newer atypical anti-psychotics (which produce less frequent EPSEs) will be associated with a lower incidence of TD [16]. However, it is important to note that the data regarding the long-term impact of Quetiapine or Aripiprazole use on TD is limited. Two studies on Quetiapine report 1-year TD rates of 2.7% and 0.74%, respectively [2]. The trial reports identify that treatment-emergent TD was reported in 0.2% of patients receiving Aripiprazole. The authors claim that this incidence was similar to that seen in placebo recipients (0.2%) [17]. It is important to note that widely used resources of medication information such as British National Formulary [18] do not recognize and report TD as a side-effect of Aripiprazole.

Tardive Dyskinesia is reported to be relatively more common amongst women, the elderly and patients who present with brain pathology. This case report reinforces the ongoing need for careful monitoring of neurological side-effects amongst patients requiring short-term or long-term use of atypical anti-psychotic agents. The risk of Tardive Dyskinesia may be declining with introduction of second generation or atypical anti-psychotic medication. However, this risk has not completely disappeared and remains a clinical concern in patients requiring anti-psychotic treatment [19]. Patients suffering from psychosis and acquired brain injury

may be at a relatively higher risk of developing antipsychotic induced Tardive Dyskinesia like presentation.

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