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CASE REPORT

Akathisia with Erythromycin: Induced or precipitated?

Ankur Sachdeva *, **Ruchika Rathee**

Department of Psychiatry and Drug De-addiction, Post Graduate Institute of Medical Education and Research, Dr Ram Manohar Lohia Hospital, New Delhi, India

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Abstract *Objective:* A 28-year-old male diagnosed with schizophrenia, maintaining well on Olanzapine, developed akathisia soon after addition of Erythromycin for Pityriasis Rosea. This prompted us to evaluate the relationship of Erythromycin and akathisia. *Method:* We report the case and the literature focusing on akathisia as a possible adverse event of Erythromycin. *Results:* Akathisia resolved after Erythromycin was stopped following 5 days of treatment. Akathisia was possibly induced or precipitated with use of Erythromycin. Possible etiological reasons of this clinically significant association are discussed. *Conclusion:* Erythromycin, by itself, may induce akathisia or precipitate akathisia in individuals by interfering with metabolism of other culprit drugs.

1. Introduction

Akathisia is an unpleasant sensation of "inner" subjective restlessness that manifests objectively as inability to sit still, lifting feet and constantly moving around (Brune, 2002). Akathisia is a well known adverse effect of treatment with antipsychotic (both first and second generation) drugs (Kumar and Sachdev, 2009). However, the term was coined in 1901 by Ladislav Haskovec, long before the introduction of antipsychotics (Berrios, 1995; Haskovec, 1901). This may suggest akathisia as an integral part of some disorders or as an adverse effect of some drugs which have not yet been investigated. Some other commonly implicated drugs are serotonin selective reuptake inhibitors (SSRIs) (Walker, 2002) and anti-emetics (metoclopramide, promethazine) (Tsuji et al., 2006).

Some other drugs such as Erythromycin, however, may induce akathisia. According to FDA reports, akathisia has been reported as a side effect of Erythromycin itself. Erythromycin may also precipitate akathisia by either increasing the blood concentration of the implicated drug or as an additive effect with another implicated drug. It then becomes difficult to pinpoint the exact cause of akathisia, especially when the drug in question is co-administered with a proven

* Corresponding author at: Department of Psychiatry and Drug De-addiction, Post Graduate Institute of Medical Education and Research, Dr Ram Manohar Lohia Hospital, Park Street, New Delhi 110001, India. Tel.: +91 9899528355.
E-mail address: drankur.rml@gmail.com (A. Sachdeva).

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culprit drug. We describe here a case of schizophrenia who was maintaining well on Olanzapine and developed akathisia soon after addition of Erythromycin.

2. Case report

A 28 year old unmarried Hindu Male, 12th Pass, resident of a nuclear family of Delhi, was admitted in the Psychiatry Department of a Tertiary Care General Hospital with history of an insidious onset, continuous illness of 6 years duration (since 2008), characterized by 2nd and 3rd person auditory hallucinations, delusion of reference and persecution, disturbed sleep, disorganized behavior (poor hygiene, collecting garbage, not changing clothes, roaming in the streets and disrobing), reduced self case and socio-occupational decline. The symptoms worsened in the last 2 years. The patient presented to Hospital in 2012 and was diagnosed with Schizophrenia. He was started on Tab. Olanzapine 10 mg/per day (gradually increased to 20 mg/per day in next 2 months) and Tab. Trihexyphenidyl 2 mg/per day. The patient improved significantly and maintained well on the same treatment for last 2 years. His Brief Psychiatric Rating Scale (BPRS) score decreased to 12/126 from 48/126. During the course of treatment, the patient developed rashes over his body and was referred to Dermatology department for evaluation. The rashes were diagnosed as Pityriasis Rosea and were treated with Tab. Erythromycin 250 mg (four times/day) and T. Cetirizine 10 mg (once daily) for 5 days. On 4th day of starting Tab. Erythromycin, the patient developed feeling of restlessness, anxiety, feeling to get up and move his limbs. He would pace around constantly. He presented to OPD again and the movements were diagnosed as Akathisia. Tab. Propranolol 20 mg/per day was started for akathisia but no improvement was reported. However, when Tab. Erythromycin was stopped after scheduled 5 days, the patient recovered spontaneously over next 3 days and the improvement persisted even after immediately stopping T. Propranolol (Barnes Akathisia Rating Scale; $4 \rightarrow 0$). The patient continues to be treated with Olanzapine (20 mg per day) and Trihexyphenidyl (2 mg per day) without any further instances of akathisia. The akathisia was supposed to be either directly induced by Erythromycin or precipitated due to concomitant use of Erythromycin with Olanzapine.

3. Discussion

Akathisia is usually induced by drugs such as antipsychotics, SSRIs and anti-emetics. Evidence from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and European First Episode Schizophrenia Trial suggests that both First Generation Antipsychotic (FGA) and Second Generation Antipsychotics (SGA) can equally cause akathisia (Kahn et al., 2008; Lieberman et al., 2005). Akathisia can be very debilitating for a person; hence it is important to properly recognize and manage the cause immediately.

Akathisia due to Olanzapine use is well documented. Olanzapine in the dose range of 5–20 mg induces akathisia in approximately 10% of the patients (8), due to blockade of striatal dopamine receptors. However, akathisia usually develops within weeks after initiation or dose increase of a neuroleptic drug. This was not the case here as patient was maintaining well on same dose of Olanzapine for past 2 years before adding Erythromycin and continues to maintain well after Erythromycin was stopped.

Erythromycin is a bacteriostatic macrolide antibiotic useful for the treatment of a number of bacterial infections. Erythromycin is an inhibitor of the cytochrome P450 system (Pai et al., 2000), which means that it can have a rapid effect on levels of other drugs metabolized by this system, which includes Olanzapine as well. Erythromycin is usually not known to cause akathisia and no published reports are available implicating the role of Erythromycin in akathisia. However, FDA reported akathisia in 34 patients taking Erythromycin between January 2004 and October 2012 out of a total of 4696 Erythromycin drug adverse event reaction reports. Since FDA receives reports of the most severe cases these numbers may therefore underrepresent the overall incidence of all the adverse events.

In the index case, the temporal relationship suggests Erythromycin as the causative molecule, but it is difficult to pinpoint the offending medication. Erythromycin may have by itself induced akathisia; however it is unlikely as the onset was within a few days of starting it. The other possibility is that Erythromycin may have increased the blood concentration of Olanzapine leading to akathisia, due to inhibition of cytochrome P450. However, Erythromycin predominantly inhibits cytochrome CYP3A4 while Olanzapine is metabolized primarily by CYP1A2 and to a lesser extent by CYP2D6 and CYP3A4. The third possibility that seems more acceptable/realistic is that Erythromycin might have precipitated akathisia in a predisposed individual already on Olanzapine, probably due to additive effect of both the compounds. Also, Olanzapine in itself is an inhibitor of cytochrome P450 CYP3A complex involved in metabolism of Erythromycin, which could have increased the serum concentration of Erythromycin. Hence, the causality may be attributed to the combined effect of both of these drugs.

It may be concluded that there are many drugs such as Erythromycin, which may induce and precipitate akathisia. Some of these drugs may be very commonly used in clinics. Hence, it is important to put in more research regarding the possibility of akathisia with these drugs and establish the possibly implicated culprit molecules. This needs large scale studies in future.

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