Case Report

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ARCHIVES OF MEDICINE
ISSN 1989-5216

2016
Vol.8 No.4:14

DOI: 10.21767/1989-5216.1000158

Benefits and Limits of Risperidone-Methylphenidate Combination in Child Psychiatry: 3 Cases

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Received date: Jul 19, 2016; **Accepted date:** Aug 19, 2016; **Published date:** Aug 26, 2016

Citation: Javelot H, Michel B, Didelot N, et al. Benefits and Limits of Risperidone-Methylphenidate Combination in Child Psychiatry: 3 Cases. Arch Med. 2016, 8:4

Abstract

Methylphenidate remains the first choice treatment for attention deficit hyperactivity disorder (ADHD), but comorbid forms with Disruptive Behaviour Disorders (DBD) are undertreated.

Methylphenidate adjunction is sometimes necessary in order to treat ADHD-related symptoms in DBD behaviors initially well-regulated with risperidone. In these situations, psychostimulant-antipsychotic combinations can be a useful strategy.

We report three cases of methylphenidate-risperidone combination in the context of our clinical experience with this bitherapy.

The cases show potential benefits to treat comorbid-ADHD with DBD with the psychostimulant-antipsychotic combination and the limits due to the risk of dyskinesia.

Keywords: Child psychiatry; Methylphenidate; Risperidone; Psychostimulant-antipsychotic combination; Attention deficit hyperactivity disorder

Abbreviations

ADHD: Attention Deficit Hyperactivity Disorder; DBD: Disruptive Behaviour Disorders; MPH: Methylphenidate; RIS: Risperidone; PDD: Pervasive Developmental Disorders; CD: Conduct Disorders

Introduction

Methylphenidate (MPH) is the first choice pharmacological drug for the treatment of ADHD because of its well-established activity on hyperactivity and inattention [1].

In child psychiatry, risperidone (RIS) is beneficial in Disruptive Behaviour Disorders (DBD) and Pervasive Developmental Disorders (PDD) among other disorders [1]. These medical indications can effectively treat a number of psychiatric childhood disorders, but the co-morbid forms are, in some cases, resistant to monotherapy [1].

Thus, although the pharmacological action of psychostimulant and antipsychotic drugs may seem to be the opposite of each other, their combination may be useful in comorbid forms of ADHD, particularly with Conduct Disorders (CD) symptoms or disorder, or PDD and DBD [1] (***see Table 1**).

During the last fifteen years, several publications have reported the benefits observed following associations between psychostimulant and antipsychotic treatment [1-6].

Bitherapies seem well-tolerated, and beneficial effects have been even found on appetite and sleep disturbances [2,3]. However, the offsetting effect of adverse effects are not always obvious and the most recent results show that the psychostimulant does not reduce the effects of antipsychotic

medication on sedation [5,7], weight and body mass index [7,8], metabolic parameters and prolactin levels [7].

Table 1 Diagnosis and sub-diagnosis reported in article, with key symptoms of DSM-IV-TR (American Psychiatric Association, 2000).

Diagnosis and Sub-diagnosis		Key symptoms
Attention-deficit and Disruptive Behavior Disorders (DBD)	Attention Deficit Hyperactivity Disorder (ADHD)	Inattention, hyperactivity, disruptive behavior, impulsivity
	Conduct Disorder (CD)	Aggression to people and/or animals, destruction of property, deceitfulness or theft, serious violations of rules
Pervasive Developmental Disorders (PDD)	Autistic Disorder, Rett's Disorder, Childhood Disintegrative Disorder, Asperger's Disorder and Pervasive Developmental Disorder Not Otherwise Specified	Autistic Disorder is characterized by impairments in social interaction and communication, restricted interests and repetitive behaviors.

However, these combinations are not exempt of risks and there seem to be more serious side effects such as dyskinesia [1]. Moreover, in a recent study, we also reported 3 cases of tachycardia in children: this symptom was not documented during monotherapy and appeared after the addition of RIS to MPH in one case and MPH to RIS in two cases.

We report here three cases involving these combinations, which are not part of the cohort of 44 patients that we have recently published [1]. In these three clinical situations, the children received: firstly RIS for the first patient or MPH in the other two situations, before bitherapy. The first two cases report the beneficial effects of the bitherapy, while the latter situation shows the onset of tardive dyskinesia after the addition of the antipsychotic drug.

These three new situations are representative, in our clinical experience, of the benefits and the limits of the bitherapies involving psychostimulants-antipsychotics.

Cases Description

Case 1

A young male patient of 10 years who is fatherless since the age of 18 months. He is addressed to the Child Psychiatry Department after a psychotherapy which lasted two years. He has relationship difficulties with his mother and at school, which seems related to an increase of impulsivity which encouraged his mother to seek consultation. In the following months, the mother learns that she suffers from breast cancer which further amplifies the difficulties with his son and leads to strong manifestations of aggression from the child. The clinical situation is improved by RIS (0.5 mg/d). The child tolerates the treatment (gain of 1 kg on the first month of treatment and stabilization afterwards) prompting physicians to increase the dosage to 1 mg/d in order to regulate residual symptoms of aggression. These attentional disturbances are downplayed by the fact that aggression decreased with RIS at 1 mg/d. The introduction of MPH 20 mg/d (MPH hydrochloride, extended-release) regulated his attentional difficulties during the day. This initial dose then increased to 30 mg/d. His learning abilities improved especially in domains such as reading and writing. The mother reported under combination therapy: a real improvement of school work, improved sleep quality hitherto disturbed and leading to the regulation of impulsivity and aggression. After a year of follow-up the bitherapy seems effective and well-tolerated.

Case 2

We report the case of a young male patient, 9 years old, who was treated during 2 years with MPH 20 mg/d (MPH hydrochloride, extended-release) because of his ADHD. The family situation is stable, but the father has ADHD himself, and is treated with MPH. With MPH 20 mg/d, the child's behaviour in class improved, but he manifested increasingly violent oppositional outbursts during which he yells, insults his parents, and hits the walls. Because of these behavioural problems, RIS is introduced at 0.5 mg/d, and the dose is increased after one month to 1 mg/d. In this context, fewer behavioural problems are observed. After one year under bitherapy, the child seemed well-stabilized. The mother reported better attentional abilities and less aggressive behaviour, probably due to bitherapy. Moreover, the quality of the child's sleep improved, and nightmares that were present when he took MPH alone disappeared. The child seemed aware of the decrease of his impulsive aggressive behaviors, and reported a newfound well-being. After one year, the bitherapy seems effective and well-tolerated. Even though he had gained 10 kg in the past year, he grew, and now his BMI is average.

Case 3

The third patient is a young male, 7 years old, with ADHD characterized by severe attentional disturbances, motor restlessness, and impulsivity. The treatment began with MPH at 10 mg/d. After two months, the dose was 20 mg/d, since attentional disturbances remained present. However, after one year, MPH alone seemed to have a modest effect on attention. Moreover, it became apparent that the child's social behaviour lacked reciprocity, and that he presented with behavioural anomalies, such as restricted interests, consistent with a PDD diagnosis. In addition to MPH, 0.5 mg/d of RIS was introduced

in order to target autistic symptoms. However, 10 days after the introduction of the antipsychotic drug, the patient presented with dysarthria, a trismus, some swallowing difficulties and an oculogyration. All these extrapyramidal symptoms were strongly suggestive of early dyskinesia. RIS was discontinued, and these symptoms regressed.

Discussion

The first case resembles the most typical clinical picture reported among 16 children that who first received RIS before switching to the bitherapy RIS-MPH, and whose cases have recently been published [1]. Antipsychotic seems to be a useful option to regulate CD-related symptoms, but hyperactivity becomes apparent when aggressive behaviours become rare. Hyperactivity was targeted by the introduction of MPH. The second case illustrates a frequent situation found in our second cohort of 28 patients which had a primary diagnosis of ADHD, treated with MPH, further clinical observations led to the identification of DBD-related symptoms which was successfully treated with bitherapy [1]. Moreover, this case also reflect previous results that show that (i) MPH is effective in the short term, but sometimes it is insufficient in the long term [9], (ii) RIS could potentiate MPH's action on ADHD symptoms [3]. The two first cases show a significant alleviation of aggressive behaviours and sleep disturbances, which are frequently found in cases treated with bitherapy [1,2].

In the first case, the sleep quality was improved after the introduction of MPH. Sleep quality improvement is less frequent under bitherapy when MPH is introduced after RIS and not otherwise [1], but this observation might be due to better regulation of impulsive and aggressive behaviours during the day. MPH-adding improve: (i) impulsivity because of its well-characterized beneficial effects on ADHD-symptoms, (ii) aggression, in line with the positive effects of MPH on aggressive and antisocial behaviours [1].

In the second case, the improvement of sleep quality can be explained by the introduction of RIS whose sedative properties are well-known and well-established in the context of MPH-RIS bitherapy [2,7]. However, this result is not consistent with other recent case reports that shows that RIS effects on sedation did not differ from placebo in a patient treated with psychostimulants [4]. The introduction of RIS to MPH also has: (i) beneficial effects on attention, in line with a previous study which described that RIS could potentiate the action of MPH on ADHD-symptoms [3], (ii) beneficial effects on aggressive behaviour, consistent with results that show the positive effects of RIS on DBD-related symptoms [1].

In the third case, autistic behaviours became apparent after the introduction of MPH. This can be interpreted as exacerbation of autistic symptoms due to MPH, although it is often prescribed, with good results, in PDD comorbid with ADHD [10]. Dyskinesia onset after RIS introduction shows that bitherapy introduction, psychotimulant-antipsychotic discontinuations, and switch from RIS to MPH are critical situations that may generate dyskinesia [1]. In 2014, Javelot et al. [1] reported one case of tardive dyskinesia with MPH-RIS combination, which was stopped by discontinuation of both drugs. Willemsen and van der wal reported a similar case with a child treated during one year with the same drugs [11]. However, stop a psychostimulant-antipsychotic combination must be managed very carefully because of the risk of dyskinesia with psychostimulants [12,13] or neuroleptic [14] discontinuations or even during switches from RIS to MPH [14-16].

Conclusion

Theses clinical situations show that bitherapy consisting of psychostimulant-antipsychotic drugs in general, and MPH-RIS more specifically, may be effective in comorbid-ADHD with DBD, but caution is necessary with its clinical management (introduction, discontinuation, and switch).

At the pharmacological level, the beneficial effects of RIS-MPH bitherapy on comorbid-ADHD with DBD can be explained by: (i) the lack of interaction with MPH, (ii) D_{2-} and $5HT_{2A}$ antagonism for aggressive symptoms, (iii) a potential contribution of psychostimulant-stimulation on D_1 and α_{2A} receptors in prefrontal cortex with the α_1 blockage of antipsychotic that can limit excessive catecholamine release [1].

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