

Letter to the Editor

Paradoxical Worsening of Attention Deficit Hyperactivity Disorder Symptoms with Methylphenidate and Clonidine Combination in a Mentally Retarded Child

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Introduction

Clonidine, an α_2 -agonist, has been used in a large number of children and adolescents in combination with methylphenidate (MPH) to provide better control of Attention Deficit/Hyperactivity Disorder (ADHD) symptoms especially hyperactivity and impulsivity, aggression and oppositionality, tics and treatment emergent side effects of MPH such as insomnia.^{1,2} Clonidine has been found safe and effective in mentally retarded (MR) children with ADHD.³ Our report describes a MR child in which ADHD and Oppositional Defiant Disorder (ODD) symptoms worsened after addition of clonidine to MPH.

Case History

Master S, an 8-year-old boy was evaluated clinically as well as on Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime Version (K-SADS-PL). He was diagnosed as having mild mental retardation (IQ 65) with ADHD-hyperactive-impulsive (HI) type, ODD and chronic motor tic disorder. No cause could be found for MR on detailed history and physical examination. History was also not suggestive of any lack of psychosocial stimulation in infancy. He was initially sent to school but he had to be withdrawn from there because of his behavioral problems.

He was started on MPH and adequate symptom control was seen with 10 mg/day of MPH in two divided doses. He was on regular follow-up and except for slight and occasional fluctuations in symptoms, remained well. No worsening of tics was observed on MPH. After about 3½ years, the dose of MPH was increased to 20mg/day in two-divided doses (body weight – 35 Kg) to control a partial relapse of ADHD symptoms. Increased dose of MPH led to almost 50% reduction in S's sleep and appetite. Therefore, dose of MPH was reduced to 15 mg and simultaneously clonidine was added and gradually increased in one week to 100 mcg/day in three divided doses in order to improve ADHD and reduce the above MPH induced adverse effects. After 1 week of the 100mcg dose of clonidine, the symptoms of ADHD and aggression worsened markedly. His aggressive behaviour became more frequent, severe and was difficult to control. His sleep and appetite also decreased further. The parents were very much frightened and upset by the above events. After 2 weeks of worsening of symptoms it was decided to re-evaluate him clinically as well as on K-SADS-PL and Hillside Behavior Rating Scale (HBRS). He fulfilled the diagnostic criteria for ADHD-HI type, ODD and chronic motor tic disorder. There was no evidence of manic symptoms, delusions or hallucinations. On HBRS (minimum score - 7 and maximum - 37) his score was 22. There

were no significant change in his blood pressure, pulse rate, temperature and body weight, also no other abnormality was detected on physical examination. Also, there was no change in school or family circumstances to explain the above worsening of symptoms. Patient was also not given any other additional medication by parents. Clonidine was tapered off in the next 5 days. His symptoms returned to baseline levels within 10 days of stopping clonidine. On reassessment on K-SADS-PL his symptoms were sub-threshold for both ADHD and ODD while the diagnosis of chronic motor tic disorder was sustained. His score on HBRS was decreased to 11. His sleep and appetite also improved without any additional medication. This improvement was maintained on 15 mg/day of MPH on subsequent follow-ups.

Discussion

The worsening of symptoms after addition of clonidine to MPH and subsequent improvement after its withdrawal suggests that the worsening could be attributed to the combination. Such an interaction has not been reported previously. A rapid decrease in clonidine plasma level due to abrupt withdrawal or poor compliance; fluctuating stimulant and clonidine plasma levels, or aggravation of an unknown clonidine-stimulant interaction by recent exercise, can cause symptoms and signs of noradrenergic overarousal, e.g. tachycardia, tachypnea, fever, anxiety, panic and acute mental status changes.⁵ In S, compliance to medications was strictly ensured by his mother and therefore the possibility that missed doses may have precipitated a withdrawal was ruled out. Also, there were no physical signs of clonidine withdrawal.

Other possible reasons for the worsening of symptoms could include physical conditions like infection (specially pertinent in children with MR), stimulant induced dysphoria (dose of MPH was increased from 10 to 20 mg/day), or rebound of symptoms as the effects of immediate release MPH subsided. However, the physical examination of S was normal; his condition did not improve after reduction of MPH dose from 20 to 15 mg/day (also later he remained well on MPH 15 mg/day); and the symptom associated with the worsening was observed throughout the day irrespective of the time of administration of drugs (also he did not have rebound symptoms before the addition of clonidine). The worsening could not be attributed to social reasons, as there was no change in school or family environment. Re-exposure to the clonidine-MPH combination was not considered on ethical grounds as the adverse effects were severe.

We are using the MPH-clonidine combination in large number of patients of ADHD with beneficial effects. We, therefore, conclude that the worsening observed in S was an unexpected and rare adverse drug-drug interaction, which cannot be explained by the knowledge we have of the mechanisms of action of these two medications. This case report aims to alert the physicians using this combination to the possibility of such worsening of symptoms in their patients.

References

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