Review Article :

Management of Attention Deficit/hyperactivity disorder (ADHD) with Methylphenidate-a brief review

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ABSTRACT:

Methylphenidate has maintained its place, as first-line choice for the pharmacotherapy of ADHD. Methylphenidate is the most commonly used psychostimulant and has proven its short and long-term efficacy in treatment of ADHD. More than 70% of the children improve with it. Excellent results particularly on cognitive manifestations of this disorder with Methylphenidate are found in most of the studies. Currently its mechanism of action and other significant aspects are being understood in a much better way. In our country its wider availability and more clinical research is suggested so that maximum number of children with ADHD can benefit from metylphenidate use.

Key words: Methylphenidate, ADHD, Psycho stimulants

INTRODUCTION:

Attention Deficit/ Hyperactivity Disorder (ADHD) hold's a special place among child and adolescent psychiatric disorders. George Still, a British Pediatrician in 1902, enumerated the description of Attention Deficit/Hyperactivity Disorder. This disorder is of great importance to the child Psychiatrist as it is one of the most commonly encountered disorders, making up to 50% of total patients in a Child Psychiatric Clinic.[1] Symptoms of ADHD may or may not come to clinical attention before school age, but parents can often report early onset of problems retrospectively. Psychostimulants have been used in the management of children and adolescents with ADHD since long. In 1937, Bradley reported the first use of Psychostimulant medication. Over the past several years, much progress has been made in understanding the actions of stimulants on children's learning and behavior.

Methylphenidate and dextroamphetamine are the most commonly used psychostimulants for ADHD, probably because of their low cost, tolerability over a broad dosage range, and safety. Methylphenidate is one of older and classical drugs for ADHD. There are several complexities and debatable issues involved in selection of a pharmacotherapy of ADHD. In an international study, an estimated 2.8% of subjects in age group of 5-18 years were receiving methylphenidate.[2] Psychostimulants continue to benefit patients with ADHD through adolescence, and adulthood, and concerns that stimulant medications prescriptions may lead to abuse seem unwarranted.[3,4] Most data have been obtained in literature from studies conducted on sample of school age children with ADHD. Role of methylphenidate across life span needs more documentation to understand its beneficial effects for patients. Still, despite considerable progress over the past two decades, much is to be learned regarding the present status of methylphenidate in treatment of Attention Deficit/ Hyperactivity Disorder. The use of methylphenidate has been fraught with controversies. The major issues were growth delay and the risk of substance abuse and affective blunting

PHARMACODYNAMICS AND MECHANISM OF ACTION

To optimize therapy for ADHD, psychiatrists should familiarize themselves with the pharmacological properties of individual drugs used to treat this disorder, adverse effects and their management, and non-responses to medications, and when to seek appropriate alternatives for these patients. For a large number of patients who are diagnosed with this ADHD, pharmacological treatment is often considered as integral part of treatment programme. Methylphenidate (MPH) remains a pharmacological treatment of first choice for children with ADHD.[5] Methylphenidate is a mild central nervous system stimulant. It is a piperidine derivative structurally related to amphetamine.[6] Methylphenidate is well absorbed from gastrointestinal tract and reaches peak plasma level in 1.5-2 hours. It has a short half-life of 2-3 hours and thus requires multiple daily dosing. With the standard preparation, the onset of behavioral effect is noted in 30-60 minutes and peak effect is noted in 1-3 hours and the effect lasts for 3-5 hours.[7] It is completely metabolized by the liver. Concentration of Methylphenidate in the brain exceeds blood concentration. Ritanilic acid is the major metabolite excreted in urine.[8] For both standard and slow release preparation the behavioral responses occur during the absorption phase and are not correlated with the plasma concentration.

Barkley reviewed fourteen studies using methylphenidate in patients with ADHD and observed a mean improvement of 75% with methylphenidate in such patients.[9] Large clinical trials directly comparing the methylphenidate from other classes of drugs are lacking. There are more than 350 double-blind placebo controlled studies (on over 3000 children) consistently demonstrating that methylphenidate lead to improved impulse control, attention, academic, social and family functioning.

More recently, with expanding field of neuro-pharmacology, a renewed interest has occurred in elucidating the mechanism of action of methylphenidate on the central nervous system. Although the precise mechanism of action of Methylphenidate in ADHD is not entirely clear, Methylphenidate is thought to affect catecholamines neurotransmitter system believed to be involved with ADHD. ADHD pathophysiology is thought to involve a pattern of decreased dopamine and increased norepinepherine neurotransmission Methylphenidate administration to animals has been shown to block norepinephrine and dopamine uptake in the striatum, hypothalamus and cortex while expediting the release of dopamine, but not norepinephrine from the striatum.11 Methylphenidate might act by correcting the catecholamine imbalance thought to be central to ADHD. The dopaminergic component of Methylphenidate action appears to be particularly crucial for its clinical effects. Methylphenidate administration alters the subcellular distribution of vesicular monoamine transporter-2 containing vesicles in rat striatum.[12] Blood flow to the Frontal and Caudate region was found to be increased when Methylphenidate was administrated to a sample of children with ADHD.[13] Oral Methylphenidate at doses within the therapeutic range significantly increase extra cellular dopamine in human brain. This coupled with findings of increased dopamine transporters in ADHD patients, provides a mechanistic framework for the therapeutic efficacy of Methylphenidate. 11-13 Methylphenidate works as a dopamine reuptake inhibitor. Methylphenidate chiefly affects the prefrontal cortex and striatum, the mechanism of action being modulation of catecholaminergic tone. Methylphenidate treatment produces an increase in dopamine signaling through multiple actions, including blockade of the dopamine reuptake transporter and amplification of dopamine response duration, disinhibition of dopamine D2 autoreceptors and amplification of dopamine tone, and activation of D1 receptors on the postsynaptic neuron. The actions of methylphenidate may also be mediated by stimulation of the noradrenergic alpha2 receptor and dopamine D1 receptor in the cortex.

CLINICAL EFFICACY:

The clinical efficacy of methylphenidate for short-term treatment of ADHD for 4-12 weeks has been well established.[3] Clinically, methylphenidate is commonly used for much longer durations, and some data exist on long-term efficacy.[4] Many studies support the efficacy of Methylphenidate in the treatment of ADHD.15-19 More than 70% of patients treated with Methylphenidate show a significant improvement in the core symptoms of ADHD.10,15 There is an immediate and often dramatic improvement in behavior.20 Attentiveness improves and interpersonal interaction including those with parents, are less confrontational. Academic performance improves but not as dramatically as behavior.21,22 Laboratory measures of attention; impulsivity, learning, information processing, short-term memory and vigilance all improve.23,24 There is significant improvement in social skills, as recorded by peer ratings, parent and teacher ratings of social function.25,26,27

Methylphenidate is indicated as integral part of total treatment program which typically includes other remedial measures (psychological, educational and social) for a stabilizing effect on children with ADHD. Many studies have been conducted using multimodal treatment approaches but the findings are conflicting one.28-35 Large number of studies have been reported from developed countries. Results of these studies revealed that combined approach is more effective than pharmacotherapy alone. A few characteristics like young age of child, clearly disturbed attention span, an average I.Q. and low level of associated anxiety, predict a better response.28 Low intelligence may predict a poor response.29 In a study of eighty four children with ADHD and conduct disorder who were treated with Methylphenidate or placebo for five weeks, both antisocial behavior and rating of ADHD improved more in the group assigned to Methylphenidate.30 Among patients who respond to drug therapy, the benefits persist over time and tolerance does not develop. However, the effects of the drug on behavior wear off quickly in two to six hours.[8] The majority of studies are short term, lasting for several months. Methylphenidate may be given safelytochildrenwithepilepsy.[31,32] In children with tic disorder and ADHD, Methylphenidate decreased disruptive behavior without necessarily worsening tics.[32,33,34] Among twenty one studies in children with ADHD, the authors reported that Methylphenidate was found to be more effective than placebo for improving overt and covert aggression related behaviours.[3]

DOSAGE:

The initial dose of standard methylphenidate is 5mgs once daily. The range of effective dose cannot be predicted by the patient's age, body mass, level of hyperactivity or measurements of plasma drug concentration.[36,37,38] Therefore the dose must be adjusted in each patient to obtain the maximum benefit. The dose may be increased every three to five days while adverse effects; behavior and academic functions are assessed through reports from parents and teachers. Academic performance may improve with lower dose, but higher doses may be required to improve motor restlessness and attention. 24 Maximum single dose of standard methylphenidate should be 20-30 mg and maximum daily dose is 60 mg. Higher doses of standard preparations have been given safely but have not been tested in clinical trials.[10] "Rebound effect" is noted with Methylphenidate i.e. worsening of behavior above baseline following the "wearing off" effect of medication. "Rebound effect" can be avoided by the use of longer acting drugs.

Extended / sustained release formulations

ADHD is a pervasive problem and its clinical features may be present in the evening, at weekend etc. Treatment needs to target at these different timings. Since 2000, there has been an increased prescription of sustained release formulation of methylphenidate for individuals with ADHD.[39] This provide consistent profile of delivery. Once-a-day sustained release (SR)formulations have been licensed in some developed and developing countries for some time.[40] In the last few years a second generation of more effective formulations (extended release formulations) has been licensed. These formulations use a range of different delivery technologies and offer smooth patterns of symptom control across the day.[41,42] These new formulations represent a major advance in the clinical management of ADHD and are popular with both patients and clinicians. As some studies show that at least 50% of patients are nonadherent with their drug therapy as prescribed over a 1-year period, long-acting formulations (administered once/day) may improve adherence.[42]

Common adverse effects

The side effects of the standard and sustained-release preparation are dose dependent. Decreased appetite is reported in approximately 80 % of children but it is mild in intensity. 10-15 % has substantial weight loss.[43,44] Insomnia is reported in 3-85% with sleep delay of about an hour is documented.[45] Abdominal pain, irritability, headache, dryness of mouth, dizziness and depression are less frequent. The weight loss may be an advantage in case of obeseoveractive children.[46] Severe adverse effects include toxic psychosis, alopecia, thrombocytopenia, Stevens-Johnson syndrome and various hypersensitivity reactions and cardiovascular complications. Methylphenidate can have significant drug interactions including inhibition of metabolism of anticonvulsants and tricyclic antidepressants. Use of Methylphenidate with clonidine and Tricyclic antidepressants leading to increased risk for significant cardiac arrhythmias has been reported.[47,48] Most common side effects can be managed by altering the time or dose of methylphenidate.

CONTROVERSIES:

a) Growth and Height of Children

Whether Methylphenidate alters growth in children has been debated.[49,50,51,52] In a controlled study, growth velocity slowed during continuous treatment with Methylphenidate.[49] In another study, the height of the boys treated with Methylphenidate was similar to that of normal boys.[50] Drug therefore may slow weight gain and growth slightly, but the long term effects are minimal. Moreover, some of the height deficit may be related to the disorder and independent of Methylphenidate intake.[10] Methylphenidate is safe and effective in children and adolescents with attention deficit/hyperactivity disorder. Research on the issue of growth suppression is lacking, mostly owing to insufficient follow-up on patient' final heights. In general, the rate of height loss seems relatively small and is reversible with withdrawal of treatment. [50,51,52]

b) Methylphenidate abuse

There is no evidence that treatment with Methylphenidate increases the risk of abuse.[53] But parents need to monitor the administration of medication carefully. Methylphenidate has similar pharmacological action like cocaine and due to this fact its activity in the brain has been studied in animals and humans. It has been postulated that the slower clearance of methylphenidate in the brain would limit drug reinforcing properties as well as its abuse potential. Psychostimulants continue to benefit patients with ADHD through adolescence and adulthood, and concerns that stimulant medication prescriptions may lead to abuse seem unwarranted.[7] There is little evidence that Methylphenidate abuse is currently a major problem. Although recent trends suggest that this could increase with the expanding production and use of methylphenidate.[54,55,56]

The appropriate assessment and management of ADHD are essential to minimize both the risk of diversion and of substance use associated with unrecognized or untreated ADHD.[54] Methylphenidate prescriptions should be monitored closely in individuals with histories of substance use. Recently twenty one studies representing 113,104 subjects have provided variable information on the pattern of the use of nonprescribed and prescribed Methylphenidate in adolescent population. The literature highlights the need to carefully monitor high-risk individuals for the use of nonprescribed stimulants and educate individuals with ADHD as to the pitfalls of the misuse and diversion of the medication.[55] Attentiondeficit/ hyperactivity disorder (ADHD) is a risk factor for subsequent substance use disorders. These studies also suggest that ADHD pharmacotherapy in childhood reduces the risk for substance use disorders. Misuse and diversion of prescribed stimulants occur among a minority of ADHD patients, especially those with conduct or substance use disorders. Extended release formulations of Methylphenidate may be less likely to be misused or diverted[56].

Newer versus older drugs

Atomoxetine was found to be effective in reducing both inattentive and hyperactive/ impulsive symptoms in a sample of children and adolescents.[57] In a small study, the efficacy of atomoxetine was found to be relatively comparable to methylphenidate.[58] Although other medications are sometimes prescribed for ADHD (e.g. tricyclic antidepressants, clonidine, buproprion, venlafaxine), these non stimulant medications has not yet been approved by FDA. Atomoxetine had received FDA approval as an ADHD treatment for children, adolescents, and adults. Unlike stimulants, which are believed to reduce ADHD symptoms through their impact on the availability of dopamine in the central nervous system, Atomoxetine exerts its effect on the neurotransmitter known as norephinphrine. Atomoxetine has no abuse potential

Non FDA approved treatment should be used after both class of FDA approved medications have been tried. These drugs are reserve drugs for those patients who do not respond or tolerate FDA approved treatments. The tricyclic antidepressants especially imipramine and desipramine were the most often prescribed non-stimulant medications for individuals with ADHD. Alpha-2 adrenergic agonists like clonidine and recently introduced guanafacine have been the focus of research in this clinical area. Bupropion and venlafaxine have been studied for their potential use in ADHD. 59,60 Bupropion is found to be less effective as Methylphenidate in ADHD.[59]

Recent treatment guidelines by the American Academy of Pediatrics recommend that two to three stimulants be tried across a full range of doses before switching to another class of medications. The stimulants have also been around for much longer, obviously, and several studies including the MTA study have documented their efficacy in symptom management over an extended period.[52] Studies on the longerterm effectiveness of Atomoxetine are needed to provide strong evidence. These will be very interesting and will likely have a significant impact on prescription pattern in ADHD.

CONCLUSION:

Methylphenidate has been widely used worldwide for the treatment of ADHD. Majority of evidence supports the efficacy and safety of methylphenidate for children and adolescents with ADHD. This produces significant improvement in attention, hyperactivity, impulse control, and aggressiveness leading to better organization of behavior, task completion and self regulation. However, like any drug, it has its limitations (e.g. 23-27% nonresponder, questionable long-term effects). Its side effects are mild and do not outweigh the benefits of drug therapy. Non FDA approved treatment should be used after both class of FDA approved medications (stimulant and non-stimulant) have been tried. New drugs approved by FDA as non-stimulants like atomoxetine are showing a breakthrough in the management of ADHD. Multimodal approach in management of ADHD is still the best choice for these patients. To date, no drug is more effective than Methylphenidate for treatment of ADHD. There is urgent need to have availability of sustained release formulation of Methylphenidate in our country for better results.

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