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Methylphenidate and Dyslipidemia

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1. Introduction

Methylphenidate is one of the drugs that has been shown to elicit behavioral sensitization (1). Methylphenidate was synthesized by Ciba chemist Leandro Panizzon. His wife, Marguerite, had low blood pressure and would take the drug as a stimulant before playing tennis. He named the substance Ritaline, after his wife's nickname, Rita (2).

Its use has increased rapidly over the years and currently the drug is often prescribed for a large span of ages from childhood through adolescence and up to adulthood, thus facilitating the study of its effect on human physiology. Therefore, there is an abundance of opportunities to study its various effects on the human organism.

Methylphenidate is a piperidine derivative, structurally related to amphetamines and acts as a CNS stimulant. Methylphenidate has been widely used since 1937 for numerous indications including attention deficit hyperactivity disorder (ADHD), narcolepsy, cataplexy (3) and conduct disorder (4) in children and adolescents as well as adults (4). Although it has been indicated for ADHD since 1957 it has gained widespread use during the last two decades (5). Methylphenidate was found to affect brain sterol metabolism in mice by inhibition of the incorporation of its precursors, acetate and glucose, into the brain and by reduction of the brain's sterol levels (6). This reduction was found to occur within 24 hours in the neuronal cellular membrane, the site of methylphenidate's action (6).

2. Risk factors of atherosclerosis and cardiovascular disease

Atherosclerosis is a slowly progressive process starting at a young age (7). Therefore, many effective measures are taken early in life to prevent future cardiovascular disease worldwide, the most important being the awareness of a proper lifestyle, including physical activity, a proper diet, and abstaining from drugs and habits that may increase the likelihood of atherosclerosis through the development of different risk factors (e.g., hyperlipidemia).

Several reports (8-9) found no association between prolonged administration (1 to 4 years) of methylphenidate to hyperactive boys regarding hematopoietic, endocrine (including blood glucose levels), hepatic or cardiovascular function. This is unlike the hypercholesterolemic effect of various psychotropic medication (see below) that can cause

hypercholesterolemia secondary to cholestasis(10). It is known that cholestasis can cause hypercholesterolemia (10). Serum cholesterol appeared to be dominantly affected by lipoprotein X. Intra-hepatic cholestasis leading to reflux of bile lipids into the blood stream and subsequent formation of lipoprotein X appears to be the mechanism (11) underlying this phenomenon .

2.1 Methylphenidate's toxicity

The therapeutic use of methylphenidate for the management of ADHD in children is constantly increasing. As therapeutic use this increases the risk of unintentional overdoses, medication errors, and intentional overdoses caused by abuse, misuse, or suicide attempts. Side effects, which include nervousness, headache, insomnia, anorexia, and tachycardia increase linearly with dose (3). Clinical manifestations of overdose include agitation, hallucinations, psychosis, lethargy, seizures, tachycardia, dysrhythmias, hypertension, and hyperthermia. Hepatotoxicity was reported in rodents (11). A possible mechanism is inhibition of cytochrome p-450 (12). There are few reports about different organ failure. These were manifested by abnormal liver function enzymes, poor urine output, hypotension, tachypnea, tachycardia, abnormal blood gases, rising serum BUN and creatinine, and hyperactive deep-tendon reflexes (13). Despite its abuse potential, there is disagreement regarding the extent to which methylphenidate is being diverted from legitimate use to abuse in children and adolescents.

Gontkovsky et al (14) reported a decrease of 26% in serum glucose values after methylphenidate initiation in a patient post- cerebellar tumour resection.

Being a neurostimulant, the possible linkage of methylphenidate to the cardiovascular system was investigated. The data are controversial. Samuels et al. (8) investigated the effect of methylphenidate on blood pressure. Their study provided evidence for a possible negative cardiovascular effect of the stimulant medication on children with ADHD. Vitiello (15) did not find clinically significant changes in cardiovascular function in the majority of cases investigated. However, Langendijk et al (16) in their review show an increase in blood pressure and heart rate among adults treated with methylphenidate as being a risk factor for cardiovascular event, and Rapport et al (17) described a transient increase in blood pressure and heart rate among children treated by methylphenidate for ADHD. This was dose dependent and easily rectified with dosage adjustment. Spivak et al (18) reported a thrombocytopenia and decreased levels of norepinephrine, dopa and serotonin in children treated for three months with methylphenidate which means inhibitory impact on platelets activation.

Heart failure due to idiopathic dilated cardiomyopathy (DCM) is uncommon in young people. Cocaine and amphetamines are known to have caused dilated cardiomyopathy (19). There are very few reports linking methylphenidate therapy to DCM. Two reports from Norway described serious cardiomyopathy in young patients treated with methylphenidate (20-21). One of them was severely obese (BMI-40). An obesity-linked susceptibility to the toxic effect of methylphenidate could, therefore, play a role in the development of DCM in this patient. This is remarkable especially with regards to the short (one year) duration of the treatment. With a BMI of 40 the above mentioned patient had suffered from extreme obesity. The hyperdynamic circulation, with increased cardiac output, thought to be a

compensatory adaptation to increased adipose tissue may, at the expense of left ventricular hypertrophy and remodeling, lead to non ischemic dilated cardiomyopathy in severe obese subjects (22, 23). This is, however, unlikely to be the only cause. Human obesity is also characterized by sympathetic nervous activation (23). The concern is that methylphenidate is the responsible agent. Although the number of patients treated with this drug is high, and the reported cardiovascular side effects are few, scientists were concerned about the serious long term results this side effect could have on children and young adults. No guidelines are available to help identify individuals prone to cardiomyopathy due to central stimulating drugs.

Cardiac adverse effects from methylphenidate have been shown to affect myocardial ultra-structure in rats. This effect was irreversible after 12 weeks (24, 25). Methylphenidate is a drug which stimulates the central nervous action and produce similar effects as amphetamines. Both drugs increase synaptic and intracellular norepinephrine and dopamine in rodents and baboons (25, 26). For amphetamine the mechanism has been shown to trigger both an increased release of catecholamines and blocking their synaptic reuptake and degradation (26-27). It is the increase in adrenergic action that is believed to be cardiotoxic over time and promote cardiomyopathy (24, 28). This can be understood by the observation that, in transgenic mice, myocardial over expression of beta-adrenergic receptors was associated with myocyte apoptosis and the development of dilated cardiomyopathy (27, 29).

3. Methylphenidate and dyslipidemia

In many cases methylphenidate is prescribed for extended periods of time, usually starting from childhood or adolescence. Therefore, in the long run any metabolic consequence of the treatment might be deleterious, especially when atherosclerosis is considered. From this perspective, it seemed essential to substantiate the potential of methylphenidate to affect lipid profile. In order to evaluate this, we first looked into the possibility that other psychotropic drugs have an impact on cholesterol and triglycerides.

Hyperlipidemia is one of the major risk factors for atherosclerosis and cardiovascular diseases (30, 31). The causes of lipid metabolism abnormalities are mainly genetic. Established causes for secondary dyslipidemia include inappropriate lifestyle, liver disease, renal disease and thyroid disease (7, 9). The various drugs that are known to affect lipid metabolism include hormones (glucocorticoids, estrogens and androgens), beta-blockers, and diuretics (3, 7, 32-40). Several psychotropic drugs were reported to cause secondary hyperlipidemia, especially carbamazepine, phenobarbital, tricyclic antidepressants (in particular amitriptyline), second-generation antipsychotic medication, mainly olanzapine but also risperidone and ziprasidone. In their extensive review Ruetsch and co-writers elaborate on weight gain induced by psychotropic medications (38). According to this and many other reports weight gain is the mainstay of the psychotropic pharmacological induced hyperlipidemia. Weight gain was found to induce dyslipidemia in correlation with dosage and duration of treatment (38). In addition to increased total cholesterol and low-density lipoprotein cholesterol (LDL-c) there was also a tendency to elevate blood pressure levels and thus enhance the impact on the development of atherosclerosis (31-34). These can aggravate health risks, including higher rate of coronary heart disease, ischemic stroke due to impaired glucose tolerance, diabetes mellitus, dyslipidemia, respiratory problems.

Weight gain appears to be most prominent with some mood stabilizers (e.g. lithium, valproate, 34-38). According to current concepts, appetite and feeding are regulated by a complex of neurotransmitters, neuromodulators, cytokines and hormones interacting with the hypothalamus, including leptin and tumor necrosis factor system (37-39). The pharmacologic mechanisms underlying weight gain are presently poorly understood: possibly the various activities at some receptor systems may induce it, but also genetic predisposition plays an important role. In addition the insulin-like effect of lithium is well known.

Weight gain has been described since the discovery and the use of the first psychotropic drugs, but seems to intensify especially with some of the second generation antipsychotic medications. Understanding of the side effects of psychotropic drugs, including their metabolic consequences (weight gain, diabetes, dyslipidemia) is essential in order to avoid, firstly, a risk of lack of compliance with the ensuing risk of relapse and re-hospitalization, and secondly, the acute, life threatening events (diabetic ketoacidocetosis and non ketotic hyperosmolar coma) and long term risk complications of diabetes and overweight (31,37,39).

Many psychotropic drugs (especially methylphenidate) were designed to be started early in childhood in order to improve various target organ, cognitive and neuropsychiatric functions. These medications appeared to be very potent and significantly changed life quality, which led to their widespread use all over the world (5). These medications are often continued for a long periods (years) and may cause unfavorable metabolic effects. Rader and Hobbs (40) reported that some of these drugs affect lipid and lipoprotein metabolism and increase or decrease atherogenicity.

Methylphenidate is the most abundantly used medication for the treatment of ADHD in all ages worldwide (5). It is well known that methylphenidate has an effect on intracellular cholesterol in the brain, but to date its effect on plasma lipid metabolism has been studied to a limited extent in clinical setting (6, 41). We recently published the results of a randomized study that examined the effect of methylphenidate on blood lipid levels (42). A total of 42 outpatients with an established diagnosis of ADHD were studied. The baseline characteristics of the study group are presented in Table 1. There were 22 males and 20 females whose median age was 16 years (range 11-31). Table 2 displays the differences in the examined parameters before and after a 3 month treatment by methylphenidate. BMI didn't change during the study period. Significant decrease was found in total cholesterol, LDL-c and triglycerides levels. Non significant changes were seen in HDL-c, apolipoprotein A and apolipoprotein B levels. The changes in Lp (a) unexpectedly turned out to be statistically significant. There were no gender-based differences in any of these parameters after adjustment according to age, nor any correlations between the lipid parameters.

This is the first investigation into the impact of methylphenidate on plasma lipid profile and atherosclerosis. The results of the current study showed that methylphenidate has a significant and positive impact on the lipid and lipoprotein profile with regard to atherosclerosis. It significantly decreases total cholesterol, triglycerides and the main atherosclerotic lipoproteins, LDL-c and Lp(a). There is no good explanation of lipid lowering mechanism. However, in contrast to other psychotropic medication it didn't cause weight gain. The possible explanation: amphetamine related agents-(including methylphenidate) increase synaptic dopamine by stimulating presynaptic release of the last

Variable	Median	Lower quartile	Upper quartile
Age (years)	16	14	22
Males	52%		
BMI	22	20	24
T-Chol(mg/ dl)	157	142	179
HDL-C(mg/ dl)	51	45	64
LDL-C(mg/ dl)	93	74	114
Trigl(mg/ dl)	76	58	100
Apo A(mg/ dl)	122	109	137
Apo B(mg/ dl)	71	56	83
Lp(a)(mg/ dl)	23	9	40

BMI,body mass index ; HDL-C, high density lipoprotein;
LDL-C, low density lipoprotein; Apo A, apolipoprotein A
Apo B, apolipoprotein B; Lp (a), lipoprotein (a).

Table 1. Patient characteristics (n = 42)

Variable	Median	Lower quartle	Upper quartle	p*= p-value
ΔBMI	0	0	0.3	0.24
Δ T-Chol (mg/ dl)	-9	-15	-3	0.0002
Δ HDL-C(mg/ dl)	2	0	4	0.1
Δ LDL-C(mg/ dl)	-5	-8	1	0.016
Δ Trigl(mg/ dl)	-8	-15	-3	0.016
Δ Apo A(mg/ dl)	-4.	-12	7	0.16
Δ Apo B(mg/ dl)	-2	-5.	5	0.6
Δ Lp(a)(mg/ dl)	-2	-5	0	0.0007
ΔnonHDLc(mg/ dl)	-11	-18	-2	0.0001

Δ-difference
* Based on Wilcoxon test.

Table 2. Differences in lipid profile and BMI parameters before and after the treatment by methylphenidate.

and cause an anorexigenic effect by changes in hypothalamic monoaminergic activity and in the anorexigenic cocaine-amphetamine –regulated transcript neuropeptide (CART) expressed in the paraventricular nucleus and hypothalamic perifornical nucleus (43, 44).

Conclusion: the presented data support some positive effects on lipid profile by decreasing total cholesterol, triglycerides, LDL-c and Lp (a). No conclusions could be reached concerning atherosclerosis.

4. Limitations

These conclusions are tentative because of the large rate of early drop outs from the studies, which may limit the validity of the results. The study was performed on a relatively small number of patients (42 patients) mostly teenagers. There is not enough data about impact of methylphenidate on adult population. The reported short term study, conducted for three

months, showed positive effects on lipid profile. However it doesn't allow us to predict whether this effect will persist and whether atherosclerosis will develop.

Further, large, well-designed trials are necessary to establish the different metabolic effects of methylphenidate

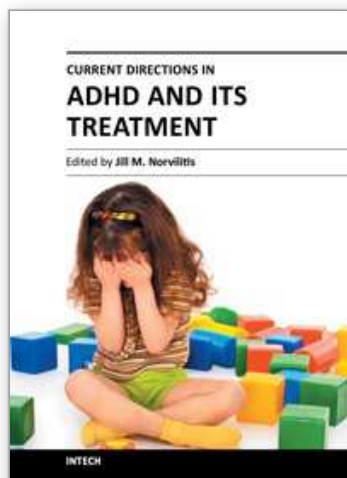
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The treatment of Attention Deficit Hyperactivity Disorder is a matter of ongoing research and debate, with considerable data supporting both psychopharmacological and behavioral approaches. Researchers continue to search for new interventions to be used in conjunction with or in place of the more traditional approaches. These interventions run the gamut from social skills training to cognitive behavioral interventions to meditation to neuropsychologically-based techniques. The goal of this volume is to explore the state-of-the-art in considerations in the treatment of ADHD around the world. This broad survey covers issues related to comorbidity that affect the treatment choices that are made, the effects of psychopharmacology, and non-medication treatments, with a special section devoted to the controversial new treatment, neurofeedback. There is something in this volume for everyone interested in the treatment of ADHD, from students examining the topic for the first time to researchers and practitioners looking for inspiration for new research questions or potential interventions.

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