Methylphenidate has mild hyperglycemic and hypokalemic effects and increases leukocyte and neutrophil counts

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Abstract
Various psychotropic drugs may affect the hematological and biochemical profiles of plasma and its metabolism. Carbamazepine, the most well-known psychotropic drug, can cause substantial hyponatremia. Methylphenidate, a piperidine derivative structurally related to amphetamines, acts as a central nervous system stimulant. The current study evaluated whether methylphenidate affects hematological and biochemical parameters of patients diagnosed with attention deficit hyperactivity disorder.

Patients undergoing treatment for attention deficit hyperactivity disorder at our Adolescent Psychiatric Clinic were enrolled in the study. Blood samples for complete blood count and common biochemical analyses were collected before patients started methylphenidate and after 3 months of continuous treatment.

Participants included 64 patients comprised the study cohort. There were 48 (75%) males and 16 (25%) females, with a median age of 16 years (range 11–31). The total median potassium level decreased by 0.6 mg/dL (P < .0001), while glucose rose by 15 mg/dL (P < .001), sodium decreased in 0.7 meq/L (P = .006). The white blood count rose by 1350 cells/μL (P < .033) due to neutrophilia, lymphocytosis and eosinophilia. Hemoglobin rose slightly by 0.1 (P = .041). Changes in calcium, phosphorus, protein, albumin, and liver enzyme levels were not significant.

The results indicate that methylphenidate may cause hypokalemia and elevated glucose, leukocyte, neutrophil, lymphocyte and eosinophil counts.

Abbreviations: ADHD = attention deficit hyperactivity disorder CNS = central nervous system.

Keywords: hyperglycemia, hypokalemia, leukocytosis, methylphenidate

1. Introduction
Methylphenidate is one of the drugs shown to elicit behavioral sensitization.[11] It was first synthesized in 1944 by Leandro Panizzon. He named the substance Ritalin, after his wife’s nickname, Rita.[2] Methylphenidate is a piperidine derivative, structurally related to amphetamines, and acts as a central nervous system (CNS) stimulant. It has been widely used since 1955 for numerous indications, including attention deficit hyperactivity disorder (ADHD), narcolepsy, cataplexy,[11] and conduct disorder in children, adolescents and adults.[1,2] Although it has been indicated for ADHD since 1957, it gained widespread use only during the last 2 decades.[3] Methylphenidate stimulates CNS activity and produces effects similar to amphetamines. Both drugs increased synaptic and intracellular norepinephrine and dopamine in rodents and baboons.[5,6] As such, it affects the biochemical profile of glucose, electrolytes, minerals, complete blood count, and liver enzymes; similar to those of catecholamines.[5–7] Therapeutic doses of amphetamines and of methylphenidate differentially increase synaptic and extracellular dopamine.[3]

There are abundant data on the impact of catecholamines on laboratory parameters, but surprisingly little comparable information on methylphenidate. Gontokovsky et al[8] reported a 26% decrease in serum glucose values after methylphenidate initiation. Several reports[5–10] found no association between prolonged administration (1–4 years) of methylphenidate on...
hematopoietic, endocrine (including blood glucose levels), hepatic, or cardiovascular functions in hyperactive boys.

Clinical manifestations of overdose include agitation, hallucinations, psychosis, lethargy, seizures, tachycardia, dysrhythmias, hypertension, and hyperthermia. Hepatotoxicity was first reported in rodents.[11] A possible mechanism for these responses is the inhibition of cytochrome P-450.[12] Various types of organ failure have also been reported. They were manifested by abnormal liver function enzymes, poor urine output, hypotension, tachypnea, tachycardia, abnormal blood gases, rising serum blood urea nitrogen (BUN) and creatinine, and hyperactive deep-tendon reflexes.[13] Spivak et al.[7] reported thrombocytopenia and decreased levels of norepinephrine, dopamine, and serotonin in children treated with methylphenidate for 3 months. These findings are indicative of an inhibitory effect on platelet activation.

Few studies have investigated the effects of methylphenidate on the lipid profile. A randomized study that examined the effect of methylphenidate on blood lipid levels[14] found significant decreases in total cholesterol, low-density lipoprotein-cholesterol, and triglyceride levels. Non-significant changes were observed in high-density lipoprotein-cholesterol, apolipoprotein A, and apolipoprotein B levels. Because of its rapidly growing use, especially among children,[10] it is important to examine the effect of methylphenidate on infancy.[11] It is not to have caused significant constitutional changes in weight, height and other parameters within that short period. The chemistry tests were analyzed with AU5800, Beckman Coulter analyzers. Sodium and Potassium were analyzed with ISE module. Glucose levels were determined in enzymatic UV test (hexokinase method). Urea levels were determined in kinetic UV test (Urease method)

2. Methods

The patients enrolled in this historical cohort (retrospective) study were from the Children and Adolescent Outpatient Psychiatric Clinic of the Tel Aviv Sourasky Medical Center. They had been referred to the clinic for suspected ADHD. Excluded were patients with other psychiatric or neurologic diseases, endocrinopathies, mental retardation, other chronic illness, or taking other medication. The candidates were evaluated, diagnosed with ADHD and prescribed treatment with methylphenidate (Ritalin).

2.1. Ethics statement

Participants received a full explanation about the nature of this 3-month study. Patients were enrolled after consent was provided by themselves or a guardian. This historical cohort study was approved by the local Ethics Committee of the Tel Aviv Sourasky Medical Center. The study was conducted in accordance with the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies.[11]

Before beginning treatment, patients provided a medical history, underwent a physical examination including blood pressure, weight, and height measurements. Blood samples were taken for a complete blood count and biochemical analysis (sodium, potassium, calcium phosphorus, magnesium, total protein, albumin, and liver enzymes) before treatment and after 3 months of continuous treatment. The period of 3 months was considered sufficient for methylphenidate to have had an effect, but not to have caused significant constitutional changes in weight, height and other parameters within that short period. The chemistry tests were analyzed with AU5800, Beckman Coulter analyzers. Sodium and Potassium were analyzed with ISE module. Glucose levels were determined in enzymatic UV test (hexokinase method). Urea levels were determined in kinetic UV test (Urease method)

2.2. Statistical analysis

Sample size was calculated with expected difference of 10% or more between 2 measurements. The required sample was about 30 patients.

Data are expressed as mean and standard deviation. Parameters were checked for normality with the Shapiro–Wilk test and most were not normally distributed. Differences between all parameters were evaluated with Wilcoxon test using Bonferroni correction for multiple testing. Variables which were highly statistically different were also found to be statistically different after applying this correction.

Logistic regression was used to identify parameters independently affected by methylphenidate. Five parameters (those with difference at $P < .0001$) were added to the model in an "enter all selected variables to the model" mode with adjustment for age,

2.3 Results

A randomized study that examined the effect of methylphenidate on blood lipid levels[14] found significant decreases in total cholesterol, low-density lipoprotein-cholesterol, and triglyceride levels. Non-significant changes were observed in high-density lipoprotein-cholesterol, apolipoprotein A, and apolipoprotein B levels. Because of its rapidly growing use, especially among children,[10] it is important to examine the effect of methylphenidate on infancy.[11] It is not to have caused significant constitutional changes in weight, height and other parameters within that short period.

## Table 1

| Laboratory value | Mean | SD | Mean | SD | Mean | SD | Lower | Upper | $P^*$ |
|------------------|------|----|------|----|------|----|-------|-------|------|
| Potassium meq/dL | 4.36 | ± 0.3 | 3.7 | ± 0.4 | 0.6 | ± 0.4 | 0.5 | ± 0.7 | < .0001 |
| Sodium meq/dL    | 139.33 | ± 3.86 | 140.0 | ± 3.6 | -0.7 | ± 1.9 | -1.2 | ± 0.2 | .009 |
| Calcium mg/dL    | 9.41 | ± 0.58 | 9.4 | ± 0.6 | 0.0 | ± 0.3 | -0.1 | ± 0.1 | .602 |
| Phosphor mg/dL   | 3.75 | ± 0.47 | 3.8 | ± 0.5 | 0.0 | ± 0.2 | -0.1 | ± 0.0 | .501 |
| ALT mg/dL        | 36.23 | ± 6.50 | 36.4 | ± 5.9 | -0.1 | ± 2.7 | -0.8 | ± 0.5 | .723 |
| AST mg/dL        | 34.72 | ± 4.13 | 40.1 | ± 29.4 | -5.4 | ± 26.8 | -12.5 | ± 1.8 | .261 |
| ALP mg/dL        | 96.44 | ± 43.0 | 95.9 | ± 42.6 | 0.5 | ± 6.5 | -1.1 | ± 2.1 | .660 |
| Hemoglobin %     | 12.85 | ± 1.09 | 12.8 | ± 1.1 | 0.1 | ± 0.3 | 0.0 | ± 0.2 | .038 |
| Lymphocytes %    | 35.16 | ± 13.1 | 36.9 | ± 10.8 | -1.7 | ± 6.8 | -3.4 | ± 0.0 | .069 |
| Neutrophils %    | 49.45 | ± 9.52 | 72.8 | ± 9.8 | -23.3 | ± 14.1 | -26.8 | ± 19.8 | < .0001 |
| Platelets $10^{12}$ | 208.89 | ± 52.9 | 205.7 | ± 49.9 | 3.2 | ± 17.4 | -3.1 | ± 1.1 | .769 |
| Eosinophils %    | 2.29 | ± 1.35 | 1.5 | ± 0.9 | 0.8 | ± 0.7 | 0.7 | ± 1.0 | < .0001 |
| Glucose          | 73.63 | ± 7.12 | 68.3 | ± 10.1 | -14.6 | ± 11.9 | -17.6 | ± 11.7 | < .0001 |

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = asparagine aminotransferase.
gender, and background diagnoses. *P* < .05 was considered significant. All statistical analyses were done with SPSS-25 software (IBM, Armonk, NY).

3. Results

A total of 83 consecutive outpatients with an established diagnosis of ADHD met the inclusion criteria and were eligible to participate in this study. Among them, 19 were excluded for various reasons, including stopping treatment, noncompliance, or lack of sufficient follow-up data. The remaining 64 patients comprised the study cohort. There were 48 (75%) males and 16 (25%) females, at a median age of 16 years (range 11–31).

Table 1 and Figure 1 display the differences between parameters before taking methylphenidate and after 3 months of methylphenidate. Body mass index did not change during the study period. The mean potassium level decreased by 0.6 mg/dL (*P* < .0001), while glucose rose by 15 mg/dL (*P* < .0001), sodium increased by 0.7 meq/L (*P* = .006) (Table 1). Changes in hemoglobin, calcium, phosphorus, protein, albumin, and liver enzyme levels, white blood count did not reach significance. Neutrophil count, lymphocytosis and eosinophilia were increased 3 months after using of methylphenidate. However, the absolute changes of the significant variables mostly fell within normal ranges. No changes in red blood cells or thrombocyte levels were found. Logistic regression (Table 2) showed that methylphenidate significantly affected blood potassium, glucose, sodium, and eosinophils (*p* < .001).

4. Discussion

Methylphenidate HCl is a CNS stimulant. The mode of therapeutic action in ADHD is not known, although it is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neurons and increase the release of these monoamines into the extra neuronal space. Worldwide, it is the most extensively used medication for treating ADHD in all age groups. A careful search of the literature revealed very little conclusive data about the impact of methylphenidate on the biochemical profile of serum glucose, sodium, potassium, calcium, phosphorus, protein, albumin, and liver enzymes. The following is an interpretation of the findings for each of these factors in the current study.

4.1. Glucose

Methylphenidate had a significant, positive effect on blood glucose levels. It increased by 22%, similar to previous studies.8,15 Data on amphetamine-like substances and hyperglycemia are inconsistent and the changes are mostly explained by emotional stress. An exception to these studies is Gontokovsky et al10 who reported a 26% decrease in serum glucose values after

![Figure 1. The differences between parameters before taking methylphenidate and after 3 months of methylphenidate.](image-url)
methylphenidate initiation. Data on the association between amphetamine-like substances and hyperglycemia are controversial as well, and elevations in serum glucose are also mostly explained by stress.\textsuperscript{[16,17]} The hyperglycemia inhibitory effect of amphetamines was also observed when given shortly before signs of stress, but not several days later.\textsuperscript{[7]}

4.2. Potassium

The mean potassium levels of the study cohort decreased by 18\% ($P < .0001$), indicative of hypokalemia. Symptomisers and their derivatives may lower serum potassium levels, but this is usually clinically significant when there is an overdose.\textsuperscript{[18]} Hypokalemia of pathological or drug-induced origin can shift the resting potential toward less negative values and thus, considerably increase the risk of torsades-de-pointes. It is therefore recommended to avoid combining sympathomimetics with hypokalemia drugs, such as amphetamines.\textsuperscript{[18–22]}

4.3. Sodium

Our results reveal minimal changes in sodium levels. There are no substantial data on the effect of methylphenidate on sodium in the literature. One study explained hyponatremia as the result of a mechanism of inappropriate anti-diuretic hormone secretion.\textsuperscript{[19]} However, others found a non-significant increase in serum sodium.\textsuperscript{[20,21]}

4.4. Calcium and phosphorous

There were no significant fluctuations in serum calcium and phosphorous associated with methylphenidate. The only publication we found regarding this association was a description of severe poisoning by the drug ecstasy, which caused hypocalcemia.\textsuperscript{[22]}

4.5. Liver enzymes

Although the results of clinical trials failed to reveal any association between methylphenidate and serum aminotransferase elevations or instances of hepatic injury, after-market reports of enzyme elevations were received from the sponsor.\textsuperscript{[11–13,22–26]} The elevations were transient, mild-to-moderate in severity, and not associated with jaundice or its symptoms.\textsuperscript{[11–13,22–26]} In addition, there were several case reports of marked serum enzyme elevations and clinically apparent acute liver injury attributed to methylphenidate given intravenously.\textsuperscript{[22]} The pattern of liver enzyme elevations was hepatocellular and the clinical phenotype was typical of acute hepatic necrosis, with rapid onset and rapid recovery.\textsuperscript{[23]} Severe amphetamine liver injury was reported as more common among patients with hepatitis C.\textsuperscript{[11–13,22–25,27]} While immunoallergic features, such as eosinophilic hepatitis were rare.\textsuperscript{[26]} Liver injury due to oral methylphenidate is usually self-limited and resolves spontaneously.\textsuperscript{[11–13]} While acute hepatic necrosis after intravenous injection of methylphenidate caused severe liver injury and even a fatal outcome.\textsuperscript{[22–23]} Eosinophilic hepatitis has also been reported in association with amphetamine derivatives.\textsuperscript{[26]}

4.6. Transaminase

Our findings did not show any significant changes in transaminases; however, there was evidence of elevated alkaline phosphatase. One explanation for this is that most of the patients were young adults and children in whom the bone alkaline phosphatase originated in growing bones. Renal function test results, for example, BUN and creatinine did not change. There have been only a few reports about different types of organ failure during overdose in the setting of intravenous methylphenidate treatment. These were manifested by abnormal liver enzymes, jaundice, poor urine output, hypotension, tachypnea, tachycardia, abnormal blood gases, increasing serum BUN and creatinine, and hyperactive deep-tendon reflexes.\textsuperscript{[13,22–25]}

4.7. Complete blood count

The current study showed 21\% elevated white blood count ($P = .014$) and 19\% neutrophilia ($P = .038$). However, the absolute changes mostly fell within normal ranges for leukocytes. Significant changes in white blood counts have been reported in the literature; mostly cases of leukocytosis stress-induced poisoning by amphetamines and neutrophilia.\textsuperscript{[22–25,27,28]} Our results revealed that erythrocyte and thrombocyte count did not rise significantly after 3 months of treatment. A limitation of this study was the relatively small sample size of 64 patients. Controlled studies of patients according to age subgroups will provide additional important information about the effect of methylphenidate on various laboratory parameters. It is worth mentioning, however, that decrease in potassium level, increase in glucose level and increase in WBC count bear a potential clinical importance. For instance, in individuals with glucose level at the high end of the normal range an elevation of glucose level by 15 mg/dL or more would establish the diagnosis of diabetes mellitus. Along the same line, toward the low end of the normal range, a decrease of 18\% or greater in potassium level increases the likelihood of cardiac arrhythmia.

5. Conclusions

Methylphenidate affects the biochemical and hematological parameters in the blood of patients diagnosed with ADHD. The results showed that it causes hyperglycemia, hypokalemia, slight hyponatremia, and elevation of total leukocyte count including, neutrophils, lymphocytes, eosinophils.

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