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Effects of Osmotic-Release Methylphenidate on Height and Weight in Children With Attention-Deficit Hyperactivity Disorder (ADHD) Following up to Four Years of Treatment

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Abstract

There is some controversy concerning \the potential negative influence of methylphenidate on growth. The authors reviewed clinical records of 187 patients with attention-deficit hyperactivity disorder under treatment with methylphenidate. The patients' weight, height, and body mass index were measured at diagnosis and during 4 years of follow-up. The dose of methylphenidate was gradually increased up to 1.31 $\pm$ 0.2 mg/kg/d. At diagnosis, mean weight value was lower than mean weight expected for age by 0.697 kg. This difference increased to 4.274 kg (at 30 months of treatment), although it subsequently decreased to 1.588 kg (at 48 months of treatment). Mean value of height was lower than expected mean height for age by 0.42 cm at diagnosis. This difference increased to 2.69 cm (at 30 months of treatment), but it subsequently decreased to 0.83 cm (at 48 months of treatment). The relationship between nutritional status and the negative effects on the height curve in those patients would require nutritional optimization to return anthropometric variables to normal.

Keywords

attention-deficit hyperactivity disorder, body mass index, height, methylphenidate, weight, ADHD

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Attention-deficit hyperactivity disorder (ADHD) is a heterogeneous behavioral disorder with an estimated prevalence of 5% to 9% within the pediatric population.[1-3] It is characterized by inattention, hyperactivity, and impulsivity and is associated with social, educational, and/or psychological deterioration. Furthermore, a variable percentage of patients manifest comorbid disorders that complicate diagnosis and treatment efficacy.[4-9]

Multimodal treatment of ADHD combines psychosocial intervention with drug therapy, which generally, involves a long-term administration of stimulant drugs.[5,9-11] In Spain, methylphenidate, in its different pharmacokinetic formulations (immediate and sustained release), is the only available stimulant drug. Methylphenidate has consistent efficacy with regard to the cardinal symptoms of ADHD and its comorbidity,[11-15] even though there is some controversy concerning the potential negative influence this drug has on growth in these patients.[16-25] Its mechanism of action is related to increased extra synaptic levels of dopamine in hypothalamus and striatum.[26,27]

This study presents an evolutionary analysis of anthropometric variables in a group of patients diagnosed with ADHD. The aim was to determine the repercussions of drug therapy with osmotic-release oral system methylphenidate during 4 years on the weight and height curve of these patients.

Methods

Patients

The study is based on data obtained from the review of the medical records of all patients diagnosed with ADHD under treatment with osmotic-release oral system methylphenidate for at least 48 months since their diagnosis. They were evaluated at the Pediatric Neurology Unit of the Navarra Hospital Complex in Pamplona, Spain, between January and December, 2009. The criteria laid down in the *Diagnostic and Statistical Manual of Mental Disorders*[28] were applied for diagnosis and classification. Patients were grouped into 2 clinical

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subtypes: those who manifest mainly attention deficit—inattentive subtype; and those with attention deficit, hyperactivity, and impulsivity—combined subtype.

The initial sample was 231 patients, but those patients who had stopped treatment during school holidays or summer periods were excluded. The resulting study sample was 187 patients.

Nutrition Study

The following variables were collected from every clinical record: sex, age, clinical subtype, and osmotic-release methylphenidate dose (mg/kg/d); as well as weight and height at diagnosis and at follow-up examinations after 6, 12, 18, 24, 30, 36, 42, and 48 months. Weight and height measurements were taken with patients wearing only underwear and no shoes. An Año-Sayol (Año-Sayol S.L., Barcelona, Spain) scale was used for weight measurement, with a measuring range of 0 to 120 kg and a precision of 100 g. Height was measured on a rigid wall-mounted stadiometer with a range 60 to 210 cm, and a precision of 0.1 cm.

Weight *z* score, height *z* score, and body mass index *z* score of each patient, as well as his or her expected (*z* score equals zero) weight and height for age and sex were calculated after every follow-up examination. The Seinaptracker (Medicalsoft Intercath S.L., University of Barcelona) computer program was used to perform these calculations. The growth charts and data tables of the Centro Andrea Prader (Zaragoza, Spain, 2002) were used as standard references. This research protocol was approved by the Ethics Committee of the Navarra Hospital Complex.

Results are expressed as means with the corresponding confidence intervals (95% CI) or standard deviation (SD). The computer program SPSS 17.0 for Windows (SPSS, an IBM Company, Chicago, Illinois) was used to perform the statistical analysis (Student *t* test, χ^2 test, and Pearson coefficient correlation).

Results

The sample was made up of 129 boys (69%) and 58 girls (31%), for a boy/girl ratio of 2.2. The combined subtype (n = 158) counted for 84.5% of the cases, whereas the inattentive subtype (n = 29) was 15.5%. The proportion of the combined subtype was significantly higher ($P < .002$) in boys (89.9%) than in girls (72.4%).

Mean age at diagnosis was 8.14 ± 1.60 years. Diagnosis was established during school age (6-10 years) in 84.5% of patients, preschool age (< 6 years) in 10.5% of patients, and adolescence (> 10 years) in 5% of patients. There were not any significant differences in age at diagnosis regarding sex (boys, 8.08 ± 1.64 years; girls, 8.29 ± 1.52 years) and clinical subtype (combined, 8.15 ± 1.64 years; inattentive, 8.08 ± 1.44 years).

Table 1 shows mean values of age, as well as osmotic-release methylphenidate dose (mg/kg/d) and body mass index (*z* scores) of these patients in every evolutionary follow-up. The daily mean dose of osmotic-release methylphenidate (mg/kg/d) was gradually increased during the follow-up period. From a mean dose of 0.89 ± 0.21 after 6 months, it reached 1.31 ± 0.2 after 48 months of follow-up ($P < .05$). Mean body mass index values (*z* score) stood significantly lower ($P < .05$) than basal value until 36 months of follow-up, and recovered subsequently.

Table 1. Mean Age of Patients, Osmotic-Release Methylphenidate Doses, and Body Mass Index Throughout Treatment Stages

Treatment Stage (patients, no.)	Age, y (SD)	Osmotic-Release Methylphenidate Dose, mg/kg/d (SD)	Body Mass Index, z score (SD)
Basal (187)	8.14 (1.60)	. . .	−0.14 (0.97)
6 mo (152)	8.66 (1.65)	0.89 (0.21)	−0.50 (0.82)*
12 mo (158)	9.18 (1.44)	0.90 (0.24)	−0.47 (0.77)*
18 mo (151)	9.69 (1.68)	0.95 (0.25)	−0.56 (0.82)*
24 mo (164)	10.01 (1.55)	1.02 (0.24)*	−0.42 (0.94)*
30 mo (149)	10.69 (1.64)	1.05 (0.23)*	−0.49 (0.98)*
36 mo (165)	11.13 (1.44)	1.24 (0.18)*	−0.45 (0.93)*
42 mo (148)	11.53 (1.51)	1.25 (0.20)*	−0.28 (0.97)
48 mo (160)	12.09 (1.50)	1.31 (0.20)*	−0.20 (0.99)

Ellipsis indicates that the category of data is not applicable.
*$P < .05$, with respect to basal value.

Table 2 displays mean values of weight and height; also shown are the differences between expected weight and height for age (when *z* score was 0). Also shown are the registered weight and height in every follow-up control (weight deficit and height deficit, respectively). In absolute terms, mean values of weight and height increased progressively. At diagnosis, mean weight value in these patients was lower than mean weight expected for age in 0.697 kg (weight deficit). This difference increased to 4.274 kg after 30 months of treatment, although it subsequently decreased and was 1.588 kg after 48 months of treatment. In the same way, mean value of height was lower than expected mean height for age in 0.42 cm (height deficit) at diagnosis. This difference widened to 2.69 cm after 30 months, but it subsequently shortened and was 0.83 cm after 48 months of treatment. There were not any significant differences regarding sex, age at diagnosis, or clinical subtype. There were no correlations between osmotic-release methylphenidate dose and weight deficit and height deficit in every follow-up control.

Figure 1 shows the changes in mean values of weight (*z* score) and height (*z* score) throughout the period of treatment. Basal value for weight (*z* score) gradually decreased during the treatment, falling to significantly lower values ($P < .05$) than basal value after 12 months. They remained low until 36 months of follow-up and subsequently recovered. Basal value of height (*z* score) also decreased gradually during treatment, falling to significantly lower values ($P < .05$) with respect to basal value after 24, 30, and 36 months of follow-up; they subsequently recovered.

Discussion

Attention-deficit hyperactivity disorder represents a potential matter of concern in health care, with relative significance because of its negative impact on the quality of life of the patient and the family environment. In addition, many

Table 2. Mean Weight and Height Values Registered and Weight and Height Deficits Throughout Treatment Stages

Treatment Stage (patients, no.)	Weight, kg (95% CI)	Height, cm (95% CI)	Weight Deficit, kg (95% CI)	Height Deficit, cm (95% CI)
Basal (187)	27.61 (26.88-28.34)	129.30 (127.97-130.63)	0.697 (0.35-1.04)	0.42 (0.01-0.83)
6 mo (152)	28.03 (27.23-28.83)	132.05 (130.68-133.42)	2.218* (1.55-2.87)	0.42 (0.01-0.08)
12 mo (158)	29.32 (28.40-30.24)	133.37 (132.23-134.51)	2.864* (2.37-3.35)	1.05 (0.65-1.45)
18 mo (151)	30.16 (29.15-31.17)	135.44 (133.91-136.97)	3.724* (3.02-4.42)	1.73 (0.98-2.46)
24 mo (164)	32.13 (31.01-33.25)	136.99 (135.81-138.17)	3.582* (2.68-4.08)	2.42* (1.75-3.08)
30 mo (149)	33.30 (32.21-34.39)	138.35 (137.22-139.45)	4.274* (3.46-5.08)	2.69* (2.01-3.17)
36 mo (165)	35.89 (34.57-37.21)	142.25 (140.87-143.63)	3.325* (2.42-4.22)	2.06* (1.38-2.74)
42 mo (148)	38.30 (37.92-38.67)	145.46 (143.90-147.02)	1.894 (1.00-2.78)	1.50 (0.78-2.22)
48 mo (160)	42.10 (40.59-43.61)	149.10 (147.60-150.60)	1.588 (0.68-2.48)	0.83 (0.41-1.25)

Abbreviation: CI, confidence interval.
*$P < .05$, with respect to basal value.

adolescents will continue to have troubles in adult life, which entail a series of labor, social, economic, and sanitary consequences.[29,30] There is no psychological and/or biological marker for this pathology, and diagnosis is based on clinical criteria.[28,31] Stimulant drugs, and specifically methylphenidate in our country, are the first line of treatment in patients diagnosed with ADHD.[4-8] This fact is supported by many clinical trials that corroborate the sustained efficacy of methylphenidate in attention and behavioral symptoms. To a large extent, the drug allows patients to optimize their familial, academic, and social situations.[9,11,13,32] Nevertheless, there seems to be a general concern about a virtual negative effect on height and weight growth.

Among the epidemiological aspects in this study, we point out that the age at diagnosis follows a normal distribution; there is a maximum incidence during school age, as well as a slight predominance of male sex (male/female ratio: 2.2) and of the combined subtype. This data matches the results reported in the references.[2,33-35] These peculiarities enabled us to consider that the random sample obtained was representative of a standard population of patients with ADHD, and therefore, there was no reason to suspect any statistical bias in the results and/or conclusions.

The condition sine qua non in this study was that the prescribed treatment had been osmotic-release methylphenidate because that was the only sustained-release preparation commercialized in Spain for a long enough time to complete an adequate follow-up. In addition, the advantages of its pharmacokinetic profile make it better than the immediate release preparation,[4-8] so it was the stimulant drug of choice at that time.

The dose prescribed in these patients was conditioned by the presentation of commercialized osmotic-release methylphenidate (18, 36, and 54 mg; 27 mg has been recently added) and, especially, by the mandatory adjustment of dose in relation to the clinical response.[36] The total daily mean dose was increased systematically throughout the follow-up in a similar way to that in previous studies.[6,10,13,15,18,37,38] In no case did we prescribe doses of osmotic-release methylphenidate that could virtually affect growth (maximum dose was 1.81 mg/kg/d)[22]; and therefore, we were always within the margin of safety and tolerability.

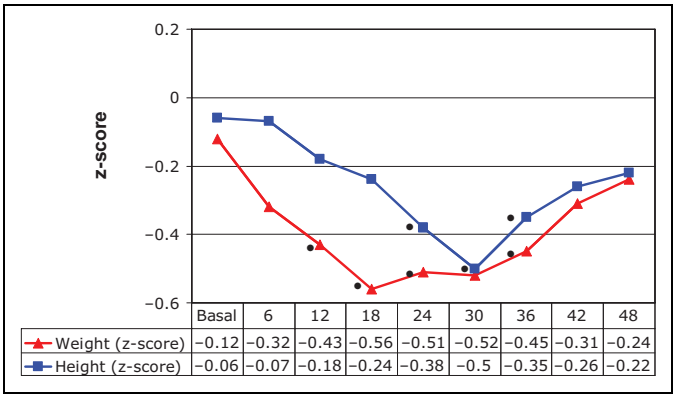

Figure 1. Changes in mean values of weight (z score) and height (z score) throughout the period of treatment.
*$P < .05$, with respect to basal value.

Mean weight and height values of patients—in absolute terms—slightly increased (14.9 kg and 19.8 cm, respectively) during the period of treatment. Nevertheless, as this period progressed, the differences with respect to expected values for age, in weight (weight deficit) as well as in height (height deficit), increased gradually, reaching the top difference values after 30 months of treatment (4.274 kg and 2.69 cm, respectively). When taking into account that initial weight and height were lower than expected for age, we could consider that a weight deficit of 3.58 kg (1.43 kg/y) and a height deficit of 2.27 cm (0.91 cm/y) would have accumulated. Nevertheless, a spontaneous progressive recovery of registered anthropometric variables was proof after 36 months of follow-up; in this way, accumulated weight and height deficit were not significant after 48 months of treatment, being 0.89 kg (0.22 kg/y) and 0.41 cm (0.1 cm/y), respectively. This evolutionary performance of anthropometric variables in this group of patients needs some considerations. On one side, the short-term observed weight and height deficit seemed to confirm the hypothesis of the negative effect of methylphenidate on the growth of these patients,[16-18,20-23,25,39] which would require us to introduce systematic registration of anthropometric variables as a mandatory measure, as clinical guidelines and

international consensus suggest.[5-9] On the other side, the medium-term recovery of anthropometric variables seemed to confirm the hypothesis of growth rebound; this means that the effects of stimulant drugs, and specifically methylphenidate, on the growth curve would be a transitory condition that attenuates as time passes by.[18, 19,24,40-42]

Although these two hypotheses might seem antagonistic, our data suggest that they could be complementary. Most of previous studies about the security and tolerability of methylphenidate refer to a synchronous effect of this drug on weight and height,[18,23,24,39] and few references point to nutrition deficit as a mechanism potentially related to growth retardation that these patients may present during treatment with methylphenidate.[22,43] A lack of temporal coincidence has been noticed in this series among slow weight and height gain, which recalls the classical concept that a nutritional deficiency (acute malnutrition) initially manifests as a weight loss and implies growth retardation when maintained for a long period of time (chronic malnutrition). This way, the growth rate would reach normality after body weight recovery. This means that the data suggest that the anorexigenic effect of methylphenidate—the maximum effect of which is observed between 18 and 30 months after the beginning of the treatment—would be the direct cause of the flattening in weight curve in these patients. Therefore, this sustained nutritional deprivation would be the main cause of proved growth retardation. The weight recovery would take place later, possibly in relation to dietary changes by families and/or pediatricians of these patients in order to counteract the nutritional aggravation during the treatment with methylphenidate. This could explain, to a great extent, the growth rebound in these patients. However, a decrease of the anorexigenic effect of methylphenidate sometime after beginning use of the drug might contribute to this event. However, the effect of stimulant medication, in this case osmotic-release methylphenidate, on growth needs to be studied prospectively and during longer periods looking at the causal mechanisms and the long-term implications for final stature.

This study has a series of methodological limitations. First, a control group has not been included because of ethical implications. Therefore, the results of weight, height, and nutritional status of the patients have been compared with infant growth curves and charts, which are generally used as reference patterns in daily clinical practice. Setting up a control group of patients with mild to moderate ADHD who were receiving no pharmacological treatment proved to be impracticable. The total number of patients in these circumstances who were followed was rather limited. Many of them finally required methylphenidate because of progressive psychosocial and/or educational deterioration, and the rest faced diagnostic uncertainty. Second, an argument could be made for the exclusion of the preschool and adolescent groups from the sample to avoid auxological variability. However, those groups were not excluded because the percentage of patients in these ages was small and their inclusion allowed the study to present an overall perspective of patients with ADHD.

In short, the present relationship between nutritional status and the negative effects on the weight and height curve in those patients under maintained treatment with osmotic-release methylphenidate requires nutritional optimization, as well as the introduction of pharmacological strategies (drug holidays) in order to return anthropometric variables to normal. Therefore, the need to impart, simultaneously with multidisciplinary treatment, nutritional education programs to the patients and/or their families should be considered, so as to avoid the nutritional problems and the consequences that might be caused by treatment with methylphenidate. In addition, the possibility of stopping or reducing doses during school holidays should be taken into account so as to contribute to lessening the negative effect of methylphenidate.

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This study was performed at the Navarra Hospital Complex, Pamplona, Spain.

Authors' Contributions

TDT participated in study design and data analysis, and wrote the first draft of the manuscript. MEYP participated in study design and data collection and analysis. FGV and PZS participated in data collection and analysis. All authors participated in manuscript preparation and approved its final version.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

This study has been approved by the Ethics Committee of the Navarra Hospital Complex, Pamplona, Spain.

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