Scientific Article

The Effect of Chronic Methylphenidate Administration on Tooth Maturation in a Sample of Caucasian Children

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Abstract

Purpose: Over the past 3 decades, methylphenidate hydrochloride (MH; brand names are Concerta, Metadate, Ritalin) has been increasingly prescribed for children and adolescents diagnosed with attention deficit hyperactivity disorder (ADHD). Previous studies have demonstrated growth suppression with chronic MH administration in children and adolescents and an association of delayed dental maturation with delayed growth. It was hypothesized that, perhaps with MH use, there is a concurrent retardation in dental development. Although there has been an abundance of research done on its effect on skeletal development, no one has examined MH's possible effects on the oral cavity—particularly dental development. The purpose of this study was to evaluate dental maturation in children who had taken MH chronically.
Methods: Forty-two Caucasian children between the ages of 7 and 15.9 years who had taken MH for a minimum of 2 years were enrolled. Their dental development was compared to that of a contemporary age- and gender-matched control sample using the Demirjian method to assess dental age.
Results: It was found that this study's population of children, who ingested an average dose of 30 mg of MH daily for a mean duration of 54 months, showed no delay in dental maturation.
Conclusions: It is concluded that, for these amounts of MH exposure, there is no effect on dental maturation. (Pediatr Dent 2005;27:292-297)

KEYWORDS: METHYLPHENIDATE, DENTAL MATURATION, RITALIN, DEMIRJIAN METHOD

More than 3 million American children have been diagnosed with attention deficit hyperactivity disorder (ADHD) and are being treated with methylphenidate hydrochloride (MH; brand names are Concerta, Metadate, Ritalin).[1]

There have been numerous studies demonstrating MH's effects on growth. Safer et al[2-4] were the first to present evidence that MH might suppress growth in ADHD children. Safer and Allen[3] found that children treated chronically with more than 20 mg/day of MH and who continued treatment into the summer months showed a significant suppression in height, in addition to a decline in weight, compared to a control group. These authors[4] also demonstrated a "growth rebound" in children who discontinued the stimulant in summer months.

Later, Loney et al[5] identified a significant relationship between the cumulative dose of MH and decrements in final height and weight. Their findings confirmed that the longer the drug treatment continues, the more severe the growth suppression. These results were shared by Mattes and Gittelman.[6] More recently, Lisska and Rivkees[7] studied 68 boys and 16 girls treated continuously with MH who were age- and time-matched with untreated biologic sibling controls living in the same household. These authors found significant differences in mean height standard deviation scores after 2 years of treatment with MH.

Since the initial findings of Safer et al,[2-4] numerous authors have expressed varied opinions regarding the persistence of growth suppression into adulthood. Satterfield et al[8] concluded that, for their population with mixed regi-

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mens during summer months, there were temporary growth deficits of little clinical significance. Klein and colleagues[9,10] confirmed a "growth rebound" with medication withdrawal, and Klein and Manuzza[10] concluded that there was no effect on final statural height due to a growth rebound after discontinuation of the stimulant. Kramer and colleagues[11] re-evaluated 97 men aged 20 to 23 who took MH for 3 years as children. As a whole, the men were not affected in height or weight, but some individuals who took higher doses or who had nausea and vomiting did exhibit growth decrements. Similarly, Spencer et al[12] identified small but statistically significant deficits in height gain in a study of 124 ADHD boys. They also noted more extremes in the affected population; 10% of the ADHD boys (compared to 1% of control boys) had deficits more than 2 standard deviations below the average of control children.

The dental literature shows mixed results when comparing dental maturity to skeletal and/or sexual maturity. It has been argued by several authors that the mechanisms controlling dental development are independent of skeletal and/or sexual maturation.[13,14] Garn et al,[15] however, stated that children who are most advanced skeletally or sexually are, for the most part, advanced dentally and vice versa. Keller[16] also concluded that dental maturation was significantly delayed in children with constitutional delay of growth and puberty (CDGP) when compared with chronological age.

In a recent study by Gaethofs et al,[17] dental age was evaluated in boys with delayed puberty and compared to a control group of healthy boys. The study population consisted of 8 boys, older than 14, diagnosed as having CDGP, delayed bone age, statural height below the third percentile for chronological age, and a testicular volume less than 4 ml. The controls were 38 healthy boys between the ages of 12 and 14 years. Dental age was measured using the Demirjian method,[18] and the results revealed that CDGP boys have a significant delay in dental maturation. The CDGP group showed a mean delay in dental maturation of 1 year, 5 months compared with non- growth-delayed children 2 years younger. Therefore, the authors support the theory that the delay of onset of puberty is responsible for the delay in dental maturation.

There has been a plethora of research documenting MH's effects on skeletal development, which can be beneficial for the dental professional interested in a child's growth and development. The dental literature, however, is lacking on MH's effects on the oral cavity—particularly dental development.

In the past, there have been multiple systems for assessing chronological age based on tooth formation. In 1985, Hagg and Matsson analyzed the accuracy and precision of 3 commonly used but very different methods[19] by: (1) Liliequist and Lundberg[20]; (2) Demirjian et al[18]; and (3) Gustafson and Koch.[21] Their results showed Demirjian's method for estimating chronological age based on assessing tooth formation to be the most reliable, due to its comparatively high accuracy and precision. In the accuracy test, the children were grouped into 3 age groups, separated by gender. Demirjian's system had only a small difference between estimated and true chronological age in the youngest group. In the 2 older groups, however, marked differences were seen and overestimation (ranging from 8 to 11 months) of chronological age was observed in both males and females. This overestimation in the older groups can most likely be explained by the fact that stages occurring earlier in life are shorter in duration than those occurring later.

Roche[22] stated that stages of short duration are more informative than those of long duration. Thus, the high degree of accuracy in the younger group is most likely due to the high number of stages with short duration during that time period. Although the Demirjian method appears to be the most accurate and precise evaluation of dental age compared to other methods, overestimation of dental age by 1 to 9 months using this system has been reported by Hagg and Matsson[19] and Staaf et al.[23]

The Demirjian data is derived from 5,447 panoramic radiographs from a French-Canadian mixed sample of girls and boys between the ages of 2.5 and 19 years. In this method, the 7 left permanent mandibular teeth are used to assess dental development using pantomographs. Tooth formation is divided into 8 stages of calcification (A to H) recognized by tooth shape, not size, and the criteria for the stages are given for each tooth with detailed written and supplementary illustrations. Each stage of the 7 teeth is given a score using methods similar to those used for assessment of skeletal maturity.[24] Standards are assigned for each gender separately. The sum of the scores (maturity score) for the 7 teeth is converted to a dental age by using the table provided in the study.[25]

This study's purpose was to evaluate dental maturation in children who have taken MH and to compare them with a group of healthy, age- and gender-matched contemporary controls.

Methods

Subjects

Forty-two Caucasian children between the ages of 7 and 15.9, who had taken MH for a minimum of 2 years at the time of exposure of a panoramic radiograph, were identified. Additional inclusion criteria for enrollment were:

1. minimum MH dose of 20 mg/day;
2. no missing permanent mandibular teeth (with the exception of third molars);
3. excellent diagnostic quality of the panoramic radiograph;
4. no prior comprehensive orthodontic treatment;
5. absence of any disorder affecting growth and/or tooth development;
6. no history of ingesting any medication affecting growth and/or tooth development.

The procedures, possible discomforts or risks, and potential benefits were explained fully to the human subjects (participant and legal guardian) involved, and their informed consent was obtained. The study was approved by the Institutional Review Board of the University of Iowa.

Forty-two healthy Caucasian children, matched for gender and age within 1 month, served as a contemporary control sample and were identified through the same clinical pool as the MH group. The inclusion criteria for the controls were identical to that of the MH group, with the exception of having no history of any MH use and no history of any long-term medication use.

Data collection

In addition to reviewing the health histories of each subject, the following pertinent information was asked of each parent of the MH group children:

1. age at start and finish of MH (month and year);
2. daily dose in milligrams;
3. months per year of MH ingestion;
4. history of any medication use and/or illnesses;
5. confirmation of normal gestation (36 weeks or more).

Each panoramic radiograph was coded to ensure that the examiner was blinded. The patients' dental age was assessed by an examiner using the method proposed by Demirjian et al.[18] A second independent examiner with extensive experience determining dental development/dental age was used for calibration. Demirjian's tables did not provide calculations for dental age beyond 16 years old. Therefore, exponential and linear fits were made to the Demirjian conversions for males aged 15 through 16 years, and extrapolations to older ages were compared. No difference was found between the 2 approaches. These extrapolations were used to assign dental age for the 4 (2 control and 2 MH) boys whose teeth had fully matured beyond the range provided for the published tables.

Statistics

Descriptive statistics were obtained for the control group and the MH group. Spearman's rank correlation test was used to test for increasing or decreasing relationships between the quantitative variables. Distribution of dental age difference score (dental age of the MH group minus dental age of the control group) between the paired control and MH data was assessed using the nonparametric Wilcoxon signed rank test for paired differences, because the data were not normally distributed. The distribution of difference scores was compared for males and females using the nonparametric Wilcoxon rank sum test.

To determine intraexaminer reliability, 20 randomly assigned radiographs were re-evaluated at a later date by the same examiner. A second independent examiner also scored 20 randomly assigned radiographs to ensure interexaminer accuracy. Cohen's kappa was used as a measure of observer agreement, both for intra- and interobserver agreement. The simple unweighted kappa was calculated to define agreement as an exact match of ratings and reflects the amount of agreement adjusted for the level of expected agreement due only to chance. It takes on the value of 1 when there is perfect agreement and equals 0 when the agreement equals that expected by chance. The closer the kappa value is to 1, the greater the agreement between the 2 ratings. Kappa coefficients of 0.4 to 0.8 are generally considered to indicate moderate agreement.

Lastly, a multiple regression model was used for the dental age difference scores to assess the importance of 3 variables (gender, age, and length of drug use) in the prediction of the dental age difference scores. A P value of less than .05 was used as a criterion for statistical significance.

Table 1. Age and Gender Distribution for Control Group			
	Mean±SD	Minimum	Maximum
Chronological age (ys; N=42)	11.61±2.00	7.00	15.92
Male (N=30)	11.90±1.97	8.17	15.92
Female (N=12)	10.91±2.00	7.00	13.33
Dental age (ys)	12.58±2.84	7.75	18.00
Male	12.75±2.81	8.75	18.00
Female	12.16±3.00	7.75	16.00

Table 2. Age and Gender Distribution and Exposure Data for MH Group			
	Mean±SD	Minimum	Maximum
Chronological age (ys; N=42)	11.61±2.00	7.00	15.92
Male (N=30)	11.90±1.97	8.17	15.92
Female (N=12)	10.90±2.00	7.00	13.33
Dental age (ys)	12.20±2.67	7.75	18.00
Male	12.45±2.79	8.15	18.00
Female	11.58±2.36	7.75	16.00
Daily MH dose (mg)	30.71±13.47		
MH exposure (mos/y)	10.48±1.49		
Total MH exposure (mos)	53.55±21.12	24.00	109.00
Male	53.83±19.98	24.00	98.00
Female	52.83±24.70	24.00	109.00

Results

Descriptive statistics for control and MH groups are listed in Tables 1 and 2. MH drug exposure data are listed in Table 2. Correlation coefficients for quantitative variables, including dental age, chronological age, and time on MH, are listed in Table 3.

Difference score

A key outcome of the study was the dental age difference score—defined as dental age score for MH subjects minus dental age score for control subjects. This was used to compare the distribution of dental age difference scores between the matched control and MH data. The mean difference score between matched pairs was -0.4 years±2.20 (SD). Thus, the mean dental age for MH subjects was almost 6 months behind matched control subjects. The median difference between matched pairs, however, was 0.00 (P=.27, corresponding to the Wilcoxon signed rank test of 0 median difference), showing that there was no difference in median dental age between the 2 groups. Ten of the 42 pairs (24%) had a difference score equal to 0. In 17 of the pairs (41%), the absolute value of the difference in dental ages was 6 months or less. The 25th percentile value of the difference score was -1.05, and the 75th percentile was 0.58 years.

Bivariate rank correlations were used to assess possible relationships between dental age difference scores and age and drug use duration. There was no evidence of a relationship between the difference score with either age (Spearman rank correlation: r=-0.04; P=.82) or length of drug use (r=-0.04; P=.78).

The data provided no evidence that the dental age difference scores differed in distribution between females and males (P=.98) by the Wilcoxon rank sum test. For females, the mean of difference score was -0.59 years with a median of 0, while for males the mean of difference score was -0.30 with a median of 0.

Regression modeling

To determine whether or not the difference score (dental age of MH group minus dental age of control group) was affected by gender, age, or length of drug use, a multiple regression model was performed. No significant relationship with the difference score was found for any of these 3 variables. Standard assumptions of the multiple regression model were assessed for validity and appeared to be appropriate.

Comparison of intraobserver ratings of dental maturity scores indicated that an excellent level of agreement was present. The simple unweighted kappa coefficient was 0.91 (95% confidence limits=0.84 to 0.98). For comparison of interobserver ratings, again an excellent level of agreement was present. The simple kappa coefficient was 0.85 (95% confidence limits=0.77 to 0.93). Overall, these highly significant (P<.001) results indicate extremely close agreement for both intraobserver and interobserver in evaluating tooth development stages on radiographs.

Discussion

Although there have been numerous studies of MH's effects on skeletal development, no one has examined the possible effects on the oral cavity—particularly dental development. The objective of this retrospective study was to investigate whether MH's reported effects on delaying growth were closely related to those of delaying dental maturation. Based on oral, written, and radiographic review, the authors identified 2 groups of gender- and age-matched subjects:

1. those who had taken at least 20 mg/day of MH for a minimum of 2 years at the time a panoramic radiograph was made;
2. those who were healthy and had not ingested any long-term medication.

This study's results showed that children who took at least 20 mg of MH daily for a minimum of 2 years (mean exposure=30 mg for 53.5 months) at the time of their panoramic radiograph showed no significant effects on dental maturation.

These results are timely for health care providers. MH has been widely used to treat ADHD for many years, along with other psychostimulants. Newer drugs such as Adderall (mixed amphetamines) have been increasingly prescribed. Recently, Health Canada has suspended marketing of Adderall XR (extended release) due to sudden unexplained death (SUD) in children taking Adderall and Adderall XR. SUD has been associated with amphetamine abuse and reported in children with underlying cardiac abnormalities taking recommended doses of amphetamines. A very small number of SUD cases has been reported in children taking Adderall who were without structural cardiac abnormalities. At this time, the Food and Drug Administration is continuing to carefully evaluate these data. In light of this information, treatment with all psychostimulants will most likely be scrutinized. Health care professionals, however, may also see trends of increased reliance on MH for ADHD.

Table 3. Correlation Coefficients Among Quantitative Variables for Control and MH Groups (N=42)		
Variable	Correlation coefficient	P
Age and dental age (control group)	0.88	<.0001
Age and dental age (MH group)	0.85	<.0001
Age and time on MH(MH group)	0.35	.024
Dental age and time on MH	0.31	.049

The Demirjian method[18] was chosen to assess dental age. Various authors[19,23] have considered this method to be the most precise and accurate for assessing dental age from 7 to 15.9 years. Overestimation of dental ages ranging from 1 to 9 months, however, has been mentioned. For this study's sample, dental age was greater than chronological age by 12 months for controls and 8 months for the MH group; this is in agreement with the results of Hagg and Matsson[19] and Staaf et al.[23] Additionally, the authors used extrapolations to assign a dental age to 2 control and 2 MH subjects whose teeth had matured beyond the range provided in the published tables. The authors expect possible inaccuracies from these procedures to have a negligible impact on this study's results because the percentage of the sample involved was very small.

As reported by Gaethofs,[17] boys diagnosed as having CDGP showed a mean delay in dental maturation of 1 year, 5 months compared with normal children 2 years younger. This study's results are distinctly different from those in terms of dental development. This discrepancy could be due to 2 reasons:

1. They had a relatively small sample size, consisting of only 8 subjects—compared to this study's 42 subjects.
2. Neither height nor weight was determined in this study, because it was a retrospective study and compiling children's past height and weight at the time of their panoramic radiographs was not possible. Thus, it is non known whether this study's MH group was delayed skeletally.

The MH group consisted of 30 males and 12 females. This male predominance is also supported in the dental literature, with ADHD most commonly seen in boys with ratios ranging from 2:1 to 10:1 and with a ratio of 6:1 being the most commonly cited. Although there was a male predilection in this study's sample, gender did not appear to have a significant influence on dental age scores.

The mean duration on MH exposure for this study's subjects was 53.55 months (4 years, 5.5 months), with a mean dosage of 30.7 mg/day. Compared to previous studies,[3,5] this duration of MH use is considerably longer, and the mean daily dose is comparable. The authors hypothesized that, if MH has an effect on dental development, they would expect to witness evidence thereof in this study's population. The data, however, did not support this hypothesis.

Conclusions

Based on this study's results, the following conclusions can be made:

1. Children and adolescents who took a mean dose of 30 mg of methylphenidate hydrochloride for a mean duration of 54 months showed no delay in dental maturation when compared to a group of healthy, age- and gender-matched contemporary controls.
2. Health care professionals should become familiar with methylphenidate, a highly prevalent prescription drug.

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ABSTRACT OF THE SCIENTIFIC LITERATURE

HEALING OF 400 INTRA-ALVEOLAR ROOT FRACTURES: EFFECT OF TREATMENT FACTORS

The aim of this retrospective investigation of 400 root-fractured permanent incisors was to study the effect of treatment factors upon healing, with special reference to the effect of (1) treatment delay; (2) effect of optimal repositioning; (3) type and duration of splinting; and (4) antibiotics on the occurrence and type of root fracture healing. Treatment delay (ie, treatment later than 24 hours after injury) did not change the root fracture healing pattern. When initial displacement did not exceed 1 mm, optimal repositioning appeared to significantly enhance both the likelihood of pulpal healing and hard tissue repair. The lowest frequency of healing was found with cap splints and the highest with fiberglass or Kevlar splints. No beneficial effect of splinting periods greater than 4 weeks could be demonstrated. The administration of antibiotics had the paradoxical effect of promoting both hard tissue between fragments and pulp necrosis. It was concluded that: (1) optimal repositioning seems to favor healing; and (2) the chosen splinting method appears to be related to healing of root fractures, with a preference to pulp healing and healing fusion of fragments to a certain flexibility of the splint and possibly also nontraumatogenic splint application.

Comments: This study confirms that optimal repositioning optimized hard tissue between fragments, lowered pulp necrosis, and a certain treatment delay (a few days) appears not to result in inferior healing. The role of antibiotics upon fracture healing is questionable. **FSS**

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