Relationship Between Amphetamine Ingestion and Gingival Enlargement

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Abstract

Purpose: The purpose of this study was to determine the relationship between amphetamine ingestion and gingival enlargement.

Methods: A total of 40 subjects were included in this study. Group 1 consisted of 20 subjects taking amphetamines and attending the dental clinic at Children's Hospital of Buffalo and The University at Buffalo School of Dental Medicine. These subjects were not taking phenytoin, cyclosporine, or calcium channel blockers. Patients with cardiovascular or hormonal disorders were excluded from the study. The information obtained from patients' parents or legal guardians were: (1) the time when the patient started taking the medication; (2) how often the patient took the medication per day; and (3) the medication's dosage. Gingival and plaque indices were also measured to assess gingival health. The Silness and Löe plaque index and modified gingival index were used. A second group of 20 healthy subjects not taking any medications was used as a control group. Gingival enlargement was evaluated clinically by one examiner and evaluated from intraoral photographs by another examiner.

Results: The results of this study demonstrated a relationship between amphetamine usage and gingival enlargement. There was a statistically significant increased prevalence ($P<.05$) of gingival enlargement in the group of patients taking amphetamines.

Conclusions: This study shows that patients taking amphetamines have an increased risk of gingival enlargement. A stringent effort to minimize gingival inflammation should be instituted, and patients should be monitored closely with more follow-up appointments than nonmedicated patients. (*Pediatr Dent.* 2004;26:396-400)

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Gingival enlargement has been shown to be induced by some types of medications such as phenytoins, cyclosporines, and calcium channel blockers. Other causes of gingival enlargement are local factors such as dental plaque and calculus, puberty, pregnancy and other associated hormonal changes, systemic diseases, and neoplastic growth. Drug-induced enlargement usually starts in the papilla and extends to the margins as it progresses.[1,2]

Phenytoin was first reported to cause gingival enlargement in 1939.[3] This medication is an anticonvulsant commonly used in the treatment of epilepsy and acts by preventing the discharge of damaged brain neural cellular excitation.[2,4] It suppresses the sodium/potassium ATPase pump, which diminishes the excitation of the affected neuron.[5,6] The mechanism in which phenytoin causes gingival enlargement is not fully understood, but one possible cause is its interference with folic acid absorption. This can lead to an alteration in the oral epithelium integrity, making the connective tissue underneath it more susceptible to bacterial products and inflammation.[2]

Cyclosporines are immunosuppressors, typically used for patients with bone marrow transplants or other organ transplants. They have an inhibitory effect on T-cells.[7] Some studies suggest the incidence of gingival enlargement in patients taking cyclosporine for an organ transplant is higher than those taking cyclosporines for a bone marrow transplant.[8]

The third group of medications known to cause gingival enlargement are the calcium channel blockers. They are used to manage cardiovascular conditions by inhibiting the calcium ion influx.[5] Some studies have suggested that their effect on the gingival tissue is dose dependent, while others could not find such a relationship.[9,10] The etiology of drug-induced gingival enlargement is not fully understood, but it is known that plaque and gingivitis can act as a predisposing factor.[11] Although no data show a correlation between this medication and gingival enlargement, some

gingival enlargement has been observed in children taking amphetamines (Adderall) at the dental department at Children's Hospital of Buffalo and at The University at Buffalo School of Dental Medicine.

Amphetamines like Adderall are usually given to children with attention deficit disorder with hyperactivity (ADHD). It should be noted there are 2 subtypes of this disorder: (1) inattention; and (2) inattention with hyperactivity.[12] ADHD is not only a childhood disease. Childhood symptoms may persist into adulthood.[13] This disorder is not managed by medications alone, but also by behavior modification.[12,14]

ADHD patients may be taking medications such as methylphenidate (Ritalin) or Adderall or may not be taking any medications at all. Historically, amphetamines were given as an antiobesity medication, but now are used for central nervous system stimulus activity, elevation of the systolic and diastolic blood pressure, and respiratory stimulation.[15,16] In children, they are prescribed to reduce hyperactivity, short attention span, and emotional problems. Adderall consists of a combination of 4 amphetamine salts: (1) d-amphetamine saccharate; (2) d-amphetamine sulfate; (3) d,1-amphetamine sulfate; and (4) d,1-amphetamine aspatate. This ingredient combination has been shown to be safe and effective in treating ADHD children.[17-19] Adderall dosage is dependent on the patient's age and the severity of the condition.

Methods

This study was conducted at the dental department at Children's Hospital of Buffalo, Buffalo, NY, and the State University at Buffalo, School of Dental Medicine, Buffalo, NY. A total of 40 subjects between the ages of 6 and 14 (mean=10.3) years participated in the study. Group 1 included 20 subjects (18 males, 2 females) taking Adderall but not taking phenytoin, cyclosporine, or calcium channel blockers. These patients had no cardiovascular, hormonal, or immune system disorders. The study included all patients taking Adderall whom the examiner saw from May 13 to December 20, 2002, and whose parents or legal guardian agreed to sign the consent. Group 2 contained 20 control subjects (17 males, 3 females) who were healthy and not taking any medications. These subjects were selected by including every other subject presenting to the dental clinic on a Tuesday or a Thursday until all 20 subjects were collected.

The subject's parent or guardian signed consent forms. A second consent was signed only by subjects over the age of 7 years. The study and consent forms were approved by both the University's and the Hospital's institutional review board. All subjects received 1 exam. The examination included:

1. a medical history review;
2. collection of data concerning the medication dosage (for group 1);
3. frequency of administration;
4. date the medication was started;
5. physician's name and address.

Evaluation of the gingival health consisted of Löe and Silness' plaque index (PI)[20] and modified gingival index (MGI).[21] Löe and Silness' grading for plaque was as follows:

1. 1=a film of plaque adhering to the free gingival margin and adjacent area of the tooth (only detected by periodontal probe);
2. 2=moderate accumulation of a soft deposit along the gingival margin (can be seen by the naked eye);
3. 3=abundance of soft matter within the gingival pocket and/or along the gingival margin;
4. 0=no plaque.

The gingival index grading was:

1. 1=mild inflammation (mild color and texture changes);
2. 2=mild inflammation (the criteria is similar to grade 1, but involves the entire marginal or papillary gingival unit);
3. 3=moderate inflammation (moderate glazing, redness, edema, and/or hypertrophy of the marginal or papillary gingival unit);
4. 4=severe inflammation (marked redness, edema, and/or hypertrophy with spontaneous bleeding) at the margin or the papilla of the gingiva;
5. 0=no inflammation.[36]

A periodontal probe was used to measure the gingival enlargement for both groups. The enlargement was measured from the cementoenamel junction:

1. 1=mild (1 mm or less);
2. 2=moderate (2-3 mm);
3. 3=severe enlargement (>3 mm);
4. 0=no enlargement.

Intraoral photographs were taken to also evaluate gingival enlargement. Photographs were taken of the facial and lingual right and left sides, anterior gingiva, and soft oral tissue of both the upper and the lower arches. All clinical examinations were carried out by one examiner. The photographs were evaluated relative to gingival enlargement by another examiner who was blind to the patient's medication. This study was designed as a cross-sectional study. The results were analyzed by making statistical comparisons (using *t* test, chi-square test, and multiple regression analysis) between the 2 groups. The comparison was based on:

1. age;
2. clinical evaluation of gingival enlargement;
3. the gingival index;
4. PI;
5. visually comparing both groups' photographs to evaluate the presence or absence of gingival enlargement.

Analyses of variance and covariance were used to evaluate the gingival enlargement within each group and its association with the patient's age, the dosage of the medication, the duration of the medication, the gingival index and the PI. The chi-square test was used to compare the gingival enlargement between the 2 groups.

Table 1. Age and Gingival Findings of the Patient Population*

	Control	Study	*P*
(N)	20	20	—
Age (ys)	10.1±0.6†	10.4±0.5	.7422
GI	0.59±0.08	0.86±0.11	.0483
PI	0.94±0.07	1.05±0.06	.2441
GE	0.55±0.14	1.15±0.17	.0081

*GI=gingival index;
PI=plaque index;
GE=gingival enlargement.
†Mean and standard error.

Table 2. Chi-square Test of Gingival Enlargement

		GE*	
Group	**No. (%)**	**Mild/ moderate (%)**	**Totals (%)**
Group 2: control	10 (50)†	10 (50) Mild: 9 (45) Moderate: 1 (5)	20 (100)
Group 1: study	4 (20)	16 (80) Mild: 9 (45) Moderate: 7 (35)	20 (100)
Totals	14 (35)	26 (65)	40 (100)

*GE=gingival enlargement. Note: There is significant association between the group and gingival overgrowth; *P*=.0467.
†Frequency and percent within group.

Results

The mean ages of groups 1 and 2 were 10.4 and 10.1 years, respectively. The duration of taking the medication ranged from 5 months to 27 months, with dosages ranging from 5 mg to 30 mg per day. Table 1 shows the studied population's demographics. In the amphetamine group (group 1), 4 patients (20%) had a score of "0" (no gingival enlargement) in the gingival enlargement index, 9 patients (45%) scored "1" (mild), and 7 patients (35%) scored "2" (moderate). In group 2 (control), 10 patients (50%) had no gingival enlargement, 9 patients (45%) had mild enlargement, and 1 patient (5%) had moderate enlargement. There was no severe gingival enlargement in either group, as shown in Table 2. Using a chi-square test, it was noted that there was a statistically significant association between the amphetamine group and gingival enlargement, (*P*=.0467).

Figures 1 and 2 show mild gingival enlargement and Figures 3 and 4 show moderate gingival enlargement, respectively, in a patient taking amphetamines. When the photographic evaluation was compared by a second examiner to the combined clinical evaluation, the correlation coefficient was 0.9. Analyses of variance and covariance were used to evaluate the gingival enlargement in both groups in association with age, gingival index, PI, and the dosage and duration of the medication (the last 2 variables were measured for group 1).

In group 1, there was a significant increase (*P*<.05) in the medication dosage and the gingival index in patients who had gingival enlargement (mild and moderate) compared to the controls. The increase in the age and the PI was not significant.

In group 2, there was an increase in age, PI, and gingival index, but it was not significant (*P*>.05). The correlations between gingival enlargement and 5 variables (age, dosage, duration, MGI, PI) in group 1 and 3 variables (age, MGI, PI) in group 2, using multiple linear regression, were statistically evaluated.

Gingival enlargement in group 1 was statistically significantly associated with the gingival index (*P*=.0022). In group 2, there was no statistically significant association (*P*>.05) between the gingival enlargement and any of the 3 variables. It was noted that there was a highly statistically significant difference in the gingival enlargement between the 2 groups (*P*=.008; Table 1). It was also noted that there was a significant difference between the 2 groups in the gingival index (*P*=.0483).

Discussion

This study demonstrated that the prevalence of gingival enlargement in patients taking amphetamines is 80% (16 out of 20 patients in group 1) and 50% in patients who are not taking any medications (10 out of 20 in group 2). The patients' ages in both groups ranged from 6 to 14 years old. The results show that patients who were taking amphetamines have a 30% greater possibility of developing gingival enlargement compared to healthy patients of the same age group. A mild form of gingival enlargement was noted in this study after 5 months of taking amphetamines, but the relationship between the gingival enlargement and the medication dosage was not significant (*P*>.05). This study also showed a significant association between gingival enlargement and the gingival index in group 1 (Figure 5). This relationship was not found in group 2. The difference in PI between groups 1 and 2 was not statistically significant, suggesting that the increase in gingival enlargement and the gingival index in group 1 may be related to medication, not plaque.

Seven additional ADHD patients taking methylphenidate (Ritalin) were examined at the same dental clinic and during the same time period when the patients taking Adderall were examined. Five of these patients had no gingival enlargement, and 2 had mild gingival enlargement. These patients were not included in the study, due to the small sample size of patients taking Ritalin. The observation of minimal gingival enlargement, however, suggests that ADHD does not ensure gingival enlargement. Providing oral hygiene instructions to ADHD patients is very challenging to both the dentist and the ADHD patients. It is difficult for these patients to follow instructions, as their short attention span limits them from performing many tasks. Therefore, it is important for the dentist to consider

Figures 1-4. Patient taking amphetamine with moderate gingival enlargement.

a different philosophy and strategy to deliver his/her message to these patients. Examples of these strategies are to:

1. show care and love to the patients;
2. use positive reinforcement;
3. give rewards;
4. discuss the problem with the parents/guardian;
5. discuss only 1 instruction per visit.

These strategies are based on the patient's age and learning development. All appointments should be early in the morning and should be kept short. ADHD patients seem to be less distracted and less stressed early in the morning. The dentist should be aware of the times when these patients are not taking their medication.

Parental involvement is also vital. The parents' responsibility includes supervision, assistance, and reminding.

Drug-induced gingival enlargement may promote the progression of periodontal disease. For this reason, the dentist must assign specific oral hygiene therapies for these patients. The regimen should include:

1. 3- to 4-month recall visits with professional prophylaxis;
2. reinforcement of oral hygiene instructions at each visit;
3. use of antibacterial mouth rinses;
4. surgical involvement in severe cases.

Teamwork should be established between the dentist and the patient's physician. The dentist must evaluate the patient's oral health periodically, and a dental regimen should be started even before the patient starts taking the

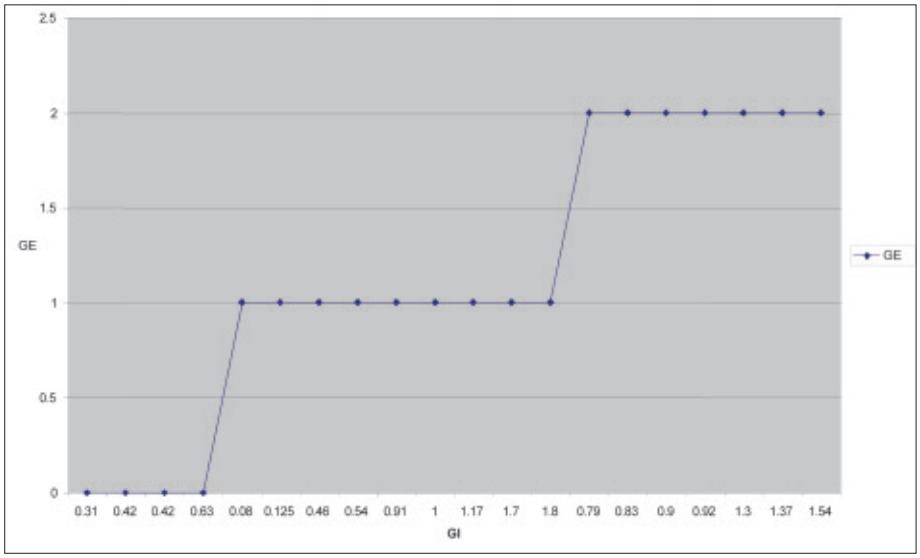

Figure 5. Relationship between GE* and GI† in group 1.
*GE=gingival enlargement.
†GI=gingival index.

medication to prevent or minimize the incidence of gingival enlargement. Future studies may be needed to compare gingival enlargement in patients taking Adderall to patients taking Ritalin, considering a double-blind approach for 2 or more examiners doing the clinical examinations.

Conclusions

1. This study found a statistically significant increase in the prevalence of gingival enlargement in patients taking amphetamine (Adderall).
2. This study showed that gingival enlargement is significantly associated with the gingival index in patients taking amphetamine.
3. This study's collected data showed that plaque index, medication duration and dosage, and the patient's age have no significant association with gingival enlargement.
4. Patients taking amphetamines (study group) have more gingivitis than healthy patients not taking amphetamines (control group).
5. Dentists have to consider the need to establish an oral hygiene regimen for patients taking amphetamines.
6. Communication between the physician of the patient receiving amphetamine and the dentist is essential, and alternate medications should be considered when gingival enlargement is problematic.
7. Future studies may be needed to compare gingival enlargement in ADHD patients who are taking amphetamine to ADHD patients who are taking medications other than amphetamine or not taking any medications.

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