C Verna
LE Hartig
S Kalia
B Melsen

Influence of steroid drugs on orthodontically induced root resorption

Authors' affiliation:
C. Verna, L.E. Hartig, S. Kalia, B. Melsen, Department of Orthodontics, School of Dentistry, Aarhus University, Aarhus, Denmark

Correspondence to:
Carlalberta Verna
Department of Orthodontics
Royal Dental College
University of Aarhus
Vennelyst Boulebard 9
8000 Aarhus-C
Denmark
Tel: +45 89424190
Fax: +45 86192752
E-mail: cverna@odont.au.dk

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Structured Abstract

Authors – Verna C, Hartig LE, Kalia S, Melsen B

Objectives – To investigate the effect of acute and chronic corticosteroid treatment on orthodontically induced root resorption.

Design – 'Split mouth' design performing orthodontic tooth movement in 64, 6-month-old male rats divided into three groups: acute (n = 22), chronic (n = 23) and control group (n = 19). Acute and chronic group received corticosteroid treatment (8 mg/kg/day) for 3 and 7 weeks, respectively, while no pharmacological treatment was performed in the control group. Performed at the Department of Orthodontics, School of Dentistry, University of Aarhus, Aarhus, Denmark.

Experimental variable – The upper left first molar was moved mesially for 21 days in all three groups with 25 g of force. Undecalcified histological sections were cut at the coronal and apical level.

Outcome measure – The number of intersections hitting resorption lacunae (ES), defined as a scalloped surface with or without cementoclasts, over the total number of intersections hitting the root surface (RS) were recorded and expressed as percentage.

Results – The acute group showed significantly more root resorption at the mesio-coronal level compared with the control and the chronic group.

Conclusion – This could be ascribed to the lack of balance between blastic activities (inhibited by the drug) and the clastic activities (enhanced or unchanged by drug administration) occurring in the initial phase of drug administration. As a consequence, a careful monitoring of patients undergoing acute corticosteroid treatment is suggested.

Key words: coricosteroid; histomorphomtery; orthodontics; rats; root resorption

Introduction

Orthodontic patients may be affected by systemic diseases that need medical treatment with drugs that could possibly affect bone metabolism. Glucocorticosteroids are commonly used to treat many different diseases because of their anti-inflammatory effect. Allergy, asthma, dermatitis and eczema are all diseases with high incidence and rapidly increasing prevalence commonly treated with corticosteroids. According to a representative investigation made by the Danish Institute for Clinical Epidemiology, the percentage of adult population affected by asthma increased from 3.2% in 1986 to 5% in 1993. Considering allergic rhinitis, hay fever and asthma together 18.1% had one or more events during 1993 (1). Steroid treatment can be in the form of oral, inhaled or topical administration depending on the disease. Systemic effects are most pronounced in oral administration, but there is growing concern and evidence of systemic effects of inhaled corticosteroids (2,3). This high prevalence and the increasing evidence of systemic effects of most forms of steroid treatment, stress the need for a better understanding of the consequences in relation to orthodontic treatment.

Corticosteroid treatment has been shown to interfere with orthodontic tooth movement rate and tissue reaction in animal studies (4–7). Controversial data are available concerning the effect of orthodontic treatment under corticosteroid treatment on root resorption. Young rabbits treated with osteoporotic doses of cortisone acetate injections (15 mg/kg) showed significantly more rapid orthodontic tooth movement and greater tendency to root resorption in the pressure areas (4). Short-term treatment with 1 mg/kg oral prednisolone in rats showed, on the contrary, significantly less root resorption, suggesting a suppressing role of the drug on clastic activities (6). Moreover, the effect of acute or chronic drug administration regime has never been investigated.

On this background, the aim of this study was to study the effect of short-term and long-term administration of therapeutic dosages of corticosteroid on orthodontically induced root resorption.

Materials and methods

Animals

Sixty-four male, 6-month-old Wistar rats, 350–500 g of body weight (Moellegaard Breeding Centre, Ejby, Denmark) were used in the experiment. They were housed paired in cages in a room with a 12:12-h artificial light cycle, at room temperature and humidity according to the National Research Council's guide for the care and use of laboratory animals. They had access to drinking water and standard laboratory rat pellets (Altromin, Brogaarden, Gentofte, Denmark) *ad libitum*.

The rats were randomly divided into three groups: a chronic group (n = 23) that received pharmacological treatment for 7 weeks (week 1–7) and orthodontic treatment for 3 weeks (week 5–7), an acute group (n = 22) that received pharmacological treatment and orthodontic treatment simultaneously for 3 weeks (week 5–7), and a control group (n = 19) without any pharmacological treatment but that received orthodontic treatment for 3 weeks (week 5–7). All animals were killed at the end of week 7.

The experimental groups received 8 mg/kg/day of methylprednisolone (Solu-medrol; Pharmacia and Uphjolm Co., Kalamazoo, MI, USA) subcutaneously every 24 h for the prescribed number of days (8). Orthodontic tooth movement was generated by the insertion of a pre-calibrated 25 g Sentalloy® (GAC, Ctr., Iship, NY, USA) orthodontic closed coil spring between the upper left first molar and upper incisors and the delivered force measured with a tension force gauge (Correx Co., Bern, Switzerland). The appliance was inserted under general anaesthesia, induced by a subcutaneous injection of 0.1 ml/100 g body weight of Immobilon® (Pherrovet, Malmø, Sweden) and reversed by the same amount of Revivlon® (Pherrovet).

To limit the influence of inter-animal variation in response to metabolic stimuli, a split-mouth design was used and the untreated contralateral side served as control side. The animals were killed with an overdose of CO_2 and the maxillae were excised.

The distance between the mesial surface of the first and the distal surface of the third molar was measured bilaterally with an electronic calliper (Digimatic; Mituioto, Telford, UK). Tooth movement was estimated by subtracting the mean of the repeated measured values

from the untreated and treated sides as described by Hong et al. (9). The error of the method based on double measurements has already been described (10).

Histology and histomorphometry

The excised maxillae were embedded undecalcified in methylmethacrylate. At the coronal level (level A) and apical level (level B) two 7 μm thick horizontal sections, 150 μm apart, were cut. The coronal and apical levels were defined using as a start the first section showing bone on the untreated side. Sections were stained with modified Goldner trichrome staining. Distance from the lower coronal section to the first apical section was 1150 μm. The mesial root of the first maxillary molar was investigated under an Olympus Light Microscope (Olympus Danmark A/S., Ballerup, Denmark) equipped with a periscope arm projecting the image onto a randomly positioned reticular grid. The number of intersections hitting resorption lacunae (ES) defined as a scalloped surface with or without cementoclasts, over the total number of intersections hitting the root surface (RS) were recorded on the mesial and distal aspects of the root at a magnification of 200×, and were expressed as percentage (Fig. 1). A minimum of 200 intersections with the RS was recorded on each section. The nomenclature of the histomorphometric evaluation was in accordance with Parfitt et al. (11).

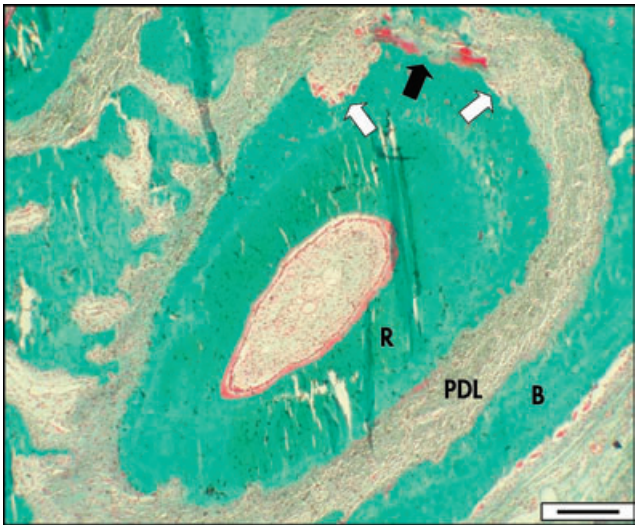

Fig. 1. Goldner trichrome-stained 7 μm section at a coronal level from the acute group. Please note the resorption lacunae (white arrow) close to the hylinized area (black arrow). B, bone; R, root; PDL, periodontal ligament. Bar = 200 μm.

Statistical analysis

A repeated measures analysis of variance was performed at the two levels and at the two sides, considering the comparison between the traded and the untreated side within each animal as repeated measurements and the pharmacological treatment as the between-animals variable.

All data were analyzed by using the statistical software SPSS for Windows (SPSS Inc., Chicago, IL, USA) and the level of significance was chosen to be 5%. The error of the method for determination of the mount of root resorption was calculated from duplicate measurements performed on 10 randomly selected rats, using Dahlberg's formula.

Results

The percentage of root resorption was in general larger on the treated than on the control side in all three groups, as shown in Table 1. Steroid administration influenced the occurrence of root resorption. The acute group showed significantly more root resorption at the mesio-coronal level that the chronic and the control group. The error of the method was 0.57% for the mesial treated side, 0.43% for the mesial untreated side, 0.70% for the distal treated side and 0.49% for the mesial untreated side and was thus considered negligible.

Discussion

As expected, root resorption was, in general, larger on the treated than in the control side, and the mesial site was in general more affected than the distal side (Table 1).

The pharmacological treatment influenced the occurrence of orthodontically induced root resorption, as the acute group showed significantly more root resorption at the mesio-coronal treated side compared with the chronic and the control group.

This finding is in agreement with a previous study performed by Ashcraft et al. in rabbits, but at osteoporotic dosage (15 mg/kg) and for a period of 14 days (4). Moreover, rabbit's molars undergoes continuous eruption, and measuring on erupting teeth may flaw

Table 1. **Percentage of root resorption in the three groups at the different levels, side, and sites**

	Acute		Chronic		Control	
	Mesial	Distal	Mesial	Distal	Mesial	Distal
Coronal						
Treated	30.03 (16.02)*	17.72 (12.41)	16.64 (11.96)	14.86 (11.59)	13.69 (12.15)	16.62 (12.23)
Untreated	6.68 (5.99)	9.02 (7.43)	7.16 (7.17)	9.92 (7.12)	9.64 (9.54)	5.57 (5.24)
Apical						
Treated	27.27 (15.75)	17.53 (19.30)	17.34 (10.34)	11.31 (10.32)	16.56 (12.24)	9.09 (8.27)
Untreated	5.27 (6.56)	8.12 (9.62)	7.31 (5.95)	6.46 (5.30)	8.05 (6.90)	1.66 (2.17)

The values are given as mean (SD).
*Significantly different from the chronic and control group ($p < 0.05$).

the results. Ong and co-workers used a lower dosage (1 mg/kg/day) in rats, and found significantly smaller length of root resorption cavities on the compression side compared with the controls (6). However, no information about root resorption occurrence was reported, and direct comparison with our data is impossible. Moreover, the treatment regime and duration was not the same. The total experimental period was only half of the period used in the present study (24 days against 49 days) and the rats only had the appliance in the mouth the last 12 days. We wanted to apply the force for at least 21 days in order to influence the metabolic state of bone and the surrounding tissues for at least one remodelling cycle, that has been evaluated to be about 21 days in 6-month-old rats (12).

The present experiment used a dose of 8 mg/kg of methylprednisolone, which is comparable with medium and high-oral doses prescribed for inflammatory diseases such as rheumatoid arthritis and renal diseases (8). However, the dose is higher than recommended for more common diseases, such as asthma. Adolescents treated with inhaled Budesonid are given about 0.8 mg/day (2), while a maximum oral dose of 10–15 mg/day has been recommend to keep the detrimental effects of bone loss minimal (13). The acute group was chosen in this study to mimic the perennial allergies such as hay fever and asthmatic attacks because of pollen, which are treated for a short time. Especially, asthma has rising prevalence and during recent years inflammation has been recognized as the predominant cause of reversible airway obstruction and airway hyper-reactivity. Evidence indicates that the frequency of asthma symptoms and the number of exacerbations are reduced, and lung function and the quality of life are improved, following treatment with inhaled corticosteroids (3) and as a result the emphasis has shifted to the early use of inhaled corticosteroids (14). The chronic group was chosen to mimic the long-term use of drugs for chronic asthma, eczema, rheumatoid arthritis, immune suppression and other chronic diseases. There is probably a greater awareness on possible side effects when steroids are taken on constant basis, but regarding root resorption we found no significant support for this. It must be kept in mind though, that 7 weeks is still a limited time interval compared with the average duration of an orthodontic treatment, but a longer treatment could not be used in the present study.

The localization of root resorption at the coronal level is consistent with previous reports (15) showing that the coronal level is the area that undergoes the largest changes after the application of a tipping force. However, we expected that the mesio-coronal and mesio-apical sites would show more root resorption, as the controlled-tipping will give compression of the periodontal ligament (PDL) and possibly hyalinization in these areas (16). The lack of significant results at the apex could be ascribed to a larger concentration of stress at the coronal than at the apical level due to the type of tooth movement achieved (17,18). Another possible explanation could be the difference in root anatomy at the apical and coronal level. At the apical level, the root was smaller, more irregular and decreased in size very rapidly close to the apex. In this situation, a slight deviation of the cutting plane will have a larger effect at the coronal level (19). Other studies used saggital cuts of the roots, looking only at the mesial and distal

aspects of the central part of the root, but at a greater apico-coronal area (4,6). We observed that root resorption cavities were often located also on the buccal and lingual aspects of the root. The choice of the transverse cutting plane allowed us to measure root resorption on all surfaces. The two cutting levels selected in this study were chosen after a pilot study conducted at our department (19), where the levels A and B were shown to be the ones where most activities occurred.

The acute group showed significantly more root resorption at the mesio-coronal treated side compared with the chronic and control group, while no difference was found on the treated sides between the chronic and control group. This could be because of the fact that in the chronic group the bone remodelling may have already increased due to secondary hyperparathyroidism during the 4 weeks of drug administration preceding the appliance insertion, whereby a new steady state may have been reached. The result is faster remodelling of bone, less hyalinization, thus leading to less remodelling of root tissues. This is in accordance with previous investigation that did not find increased amounts of root resorption in animals with increased bone turnover (20–22). Only Engström et al. (23) found an increased amount of root resorption in hypo-calcemic rats, but they did not quantify their observations. The occurrence of root resorption in the acute group could be ascribed to the lack of balance between formation activities (inhibited by the drug) and the resorption activities (enhanced or unchanged by drug administration) occurring in the initial phase of drug administration (24,25). This would lead to a longer formation phase in the remodelling cycle with a following larger amount of osteoid tissue. Unmineralized substances cannot be resorbed by osteoclasts. The balance between resorption activities on the alveolar bone and on the RS sides would be, in this case, in favour of more root resorption.

In the present study, corticosteroids were given at therapeutic doses. The amount of root resorption was studied after 3 weeks of orthodontic tooth movement, and turned out to be significantly increased at the coronal level in the acute group but not on the chronic one.

Increased amount of root resorption can be expected in patients using short-term corticosteroid. As asthma and other allergic symptoms are in fact often treated in an acute manner and for shorter periods of time, the orthodontist need to be particularly aware of the increased risk of root resorption in this group of patients.

The clinical consequences could be to induce a passive treatment phase during the periods where steroids are administered. Increased frequency of radiographs to control for root resorption may also be indicated, especially in patients who for other reasons are prone to root resorption. Another possible option may be, if possible, to postpone the start of orthodontic treatment when the acute phase of the disease is finished.

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