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Quantification of Dental Erosions in Patients With GERD Using Optical Coherence Tomography Before and After Double-Blind, Randomized Treatment With Esomeprazole or Placebo

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Abstract

Objectives—Dental erosion, the chemical dissolution of enamel without bacterial involvement, is a rarely reported manifestation of gastroesophageal reflux disease (GERD), as well as of recurrent vomiting and dietary habits. It leads to loss of tooth substance, hypersensitivity, functional impairment, and even tooth fracture. To date, dental erosions have been assessed using only very basic visual methods, and no evidence-based guidelines or studies exist regarding the prevention or treatment of GERD-related dental erosions.

Methods—In this randomized, double-blind study, we used optical coherence tomography (OCT) to quantify dental tissue demineralization and enamel loss before and after 3 weeks of acid-suppressive treatment with esomeprazole 20 mg b.i.d. or placebo in 30 patients presenting to the Berne University Dental Clinic with advanced dental erosions and abnormal acid exposure by 24-h esophageal pH manometry (defined as >4% of the 24-h period with pH < 4). Enamel thickness, reflectivity, and absorbance as measures of demineralization were quantified by OCT before and after therapy at identical localizations on teeth with most severe visible erosions as well as several other predefined changes in teeth.

Results—The mean±s.e.m. decrease of enamel thickness of all teeth before and after treatment at the site of maximum exposure was 7.2±0.16 μm with esomeprazole and 15.25±0.17 μm with placebo (P =0.013), representing a loss of 0.3% and 0.8% of the total enamel thickness,

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respectively. The change in optical reflectivity to a depth of 25 μm after treatment was −1.122 ±0.769 dB with esomeprazole and +2.059±0.534 dB with placebo (P = 0.012), with increased reflectivity signifying demineralization.

Conclusions—OCT non-invasively detected and quantified significantly diminished progression of dental tissue demineralization and enamel loss after only 3 weeks of treatment with esomeprazole 20 mg b.i.d. vs. placebo. This suggests that esomeprazole may be useful in counteracting progression of GERD-related dental erosions. Further validation of preventative treatment regimens using this sensitive detection method is required, including longer follow-up and correlation with quantitative reflux measures.

Introduction

Repeated or prolonged exposure of teeth to acid leads to selective dissolution of specific components of the tooth surface, with eventual loss of tooth substance, hypersensitivity, functional impairment, and even tooth fracture. Dissolution of tooth enamel occurs at a pH of 5.5 and below (1). Dental erosions, the chemical dissolution of enamel without bacterial involvement, are permanent and potentially disfiguring and functionally disabling. However, if enamel demineralization is detected sufficiently early, the enamel framework can possibly be remineralized using oral regimes and preventative modifications in diet, behavior or medication, which can be instituted before damage becomes irreversible (2,3). Saliva contains several minerals, such as calcium and phosphate, which undergo exchange with the surface enamel, allowing demineralization or remineralization to a steady state of equilibrium.

Raised acid presence in the mouth mainly results from dietary, psychiatric, and behavioral factors, and there is increasing evidence implicating gastroesophageal reflux (GERD) (4–10). Limited data exist on the epidemiology, pathophysiology, or treatment of the oral manifestations of GERD, but a correlation between gastroesophageal reflux and dental erosions has been shown in a few earlier publications (11,12). In patients with dental erosions, GERD has been shown in 25–83 % of patients, often affecting children, and between 17 and 68% of patients with symptomatic GERD have dental erosions (6–8,13–16). Patients with reduced saliva levels because of medication, chemotherapy, or radiotherapy are also prone to dental demineralization (17). Bulimia nervosa is associated with dental erosion due to repeated exposure of the dentition to acidic substances during regurgitation of stomach contents (18). No evidence-based treatment guidelines exist for reflux-related dental erosion and no controlled studies with acid inhibitors have, to our knowledge, been reported. Proton pump inhibitors are very effective and safe for the treatment of GERD and are used in other extra-oesophageal complications of GERD, such as chronic cough and laryngitis (19–24). Esomeprazole has been shown to be the most effective of proton pump inhibitors, both in standard as well as in maintenance treatment doses (21–23).

Detection of demineralization and quantification of tooth substance loss by dental clinicians currently relies on visual and tactile examination, supported by radiographic data. However, with these subjective, semiquantitative techniques, dental erosions are usually diagnosed when substantial enamel loss has already occurred. Optical coherence tomography (OCT) is

a new high-resolution optical technique that permits minimally invasive imaging of near-surface abnormalities in complex tissues, provides real-time structural imaging, and is based on low coherence interferometry using broadband light (24–26). Cross-sectional images of tissues are constructed in real time, at near histological resolution. Although some research has been reported in ophthalmologic, dermatologic, gastrointestinal, gynecological, cardiac, and other OCT applications, (27) the little research that has been reported in the oral cavity has focused predominantly on oral malignancy, periodontal disease, and caries (28–32). Our preliminary data using OCT and a simulated GERD model in extracted teeth show early changes in enamel thickness due to chronic GERD that are potentially greater than 50 μm, whereas the variability of the technique between repeated measurements at maximum resolution levels is below 10% (33). In this study we used OCT to quantify tooth substance loss as well as changes in optical reflectance and absorbance of dental hard tissues as measures of demineralization before and after 3 weeks of esomeprazole (20 mg b.i.d.) or placebo given in double-blind randomized manner. Our hypothesis was that enamel loss and the change in optical signal would differ between the placebo and treatment groups.

Methods

Protocol and patients

Thirty successive patients with advanced dental erosions referred from the University of Berne Dental Hospital for evaluation of GERD as an underlying cause and with abnormally increased reflux as determined by 24-h ambulatory esophageal pH-metry were included in this randomized, double-blind study using OCT for the quantification of dental enamel changes before and after 3 weeks of gastric acid inhibition with esomeprazole (20 mg) vs. placebo b.i.d. Inclusion criteria were as follows: a minimal age of 18 years, dental erosions with Lussi score > 1 (see Table 1), exclusion of other causes for dental erosions (diet, psychiatric, bruxism, salivary abnormalities, vomiting), written patient informed consent, and documentation of increased gastroesophageal reflux defined as more than 4% of the 24h esophageal pH-metry period with a pH < 4 before the start of the study (34). Main exclusion criteria were as follows: the use of any acid-inhibiting drugs, new dental treatments or a substantial change in diet within 2 weeks of the start of or during the study allergy to esomeprazole and congenital dental defects. Forty-one patients were screened for study inclusion. Eight declined study participation for personal reasons and three did not fulfil the pH-metric reflux criteria.

The degree of dental erosions was visually quantified within 7 days following screening on the first study day by an experienced dental assessor (JV) using the Lussi ratings (Table 1) and photographed (34). A researcher blinded to the results of the visual scoring then performed the OCT measurements (see below). The severity of GERD symptoms was assessed using the validated Reflux Disease Questionnaire (35).

Assignment and masking

Following completion of these preliminary tests, patients were randomized using a computer-generated list in a 1:1 ratio to either esomeprazole 20 mg b.i.d. (Nexium, AstraZeneca AG, Zug, Switzerland) or placebo b.i.d. p.os. taken 10–15 min before breakfast

and dinner for 3 weeks. Patients completed the Reflux Disease Questionnaire, drug-intake and adverse event diaries during and at the end of the treatment period. Identical tests to those performed before the study were performed after completion of the double-blind 3-week treatment period. Follow-up for completion of adverse event data collection was performed between 5 and 7 days after the end of treatment.

OCT technique

On study days, patients were permitted to eat and drink up to 60 min before imaging. They then brushed their teeth with a standard soft commercial toothbrush and toothpaste and flossed directly before the imaging. Subsequently, only consumption of still water was allowed until completion of the imaging.

Optical coherence tomography measurements were performed using the commercially available Niris OCT console and imaging probe (Imalux, Cleveland, OH), which allows real-time video rate imaging speed, simultaneous OCT and CCD imaging channels, three-dimensional volumetric imaging and surface profiling capability at an imaging depth of up to 50 μm. The imaging system has approximately 8–15 μm depth and 20 μm lateral resolution. Polarization sensitive optical coherence tomography was not used in this study. We used time-domain OCT because it is far less expensive, considerably more user-friendly and reliable, and also available as Food and Drug Administration-approved medical device with a clinical imaging probe. A primary aim of this study was to maximize innovation while remaining directly clinically relevant.

The imaging location and angle were standardized to ensure accurate colocalization at subsequent imaging events by inserting the probe into fitted holes drilled into a 5–7 mm thick dental impression previously made of each patient's upper and lower teeth using President impression material (Coltene AG, Altstätten, Switzerland). A very thick coat of impression material was used to ensure accurate directional relocalization of the imaging probe at multiple imaging events. The holes were drilled to a diameter of 3 mm, corresponding to the exact diameter of the imaging probe to ensure a snug fit for accurate relocalization of the imaging probe. Imaging was performed at the following sites: (1) upper and lower teeth—right side: labial central incisor, canine, first molar—lingual lateral incisor, first premolar, first molar. (2) Upper and lower teeth—left side: labial lateral incisor, first premolar, first molar—lingual central incisor, canine, first molar, and (3) any additional teeth with severe visible erosions. The lower border of the drill-hole was placed one-third of tooth crown length up from the incisal edge, and mid-buccally except where there was a mid-buccal fissure. This was avoided by placing the entire drill-hole mesial to the fissure. The actual scanning time at each location was 1–5 s. Each scan was visually checked for high image quality and repeated, if required.

After imaging, the following measurements were extracted from the OCT data: (1) enamel thickness, (2) backscattering signal as characterized by the OCT-detected optical signal at specific surface and subsurface locations. Variables 1 and 2 were measured by superimposing a grid on the OCT image and measuring from a defined location on the enamel–dentin junction. An obvious anatomical feature on the enamel–dentin junction, such as an irregularity, protrusion or indentation was selected and recorded as baseline imaging

landmark for each tooth. Four separate measurement locations were chosen for each tooth. These were spaced at approximately 1 mm intervals along the enamel–dentin junction. Backscattering signal was determined directly from the optical scan data by using proprietary software from the Imalux system to quantify optical signal at 1 pixel increments on individual images. Optical measurements were carried out at the same locations as the enamel thickness determinations.

Analysis

Our pilot data showed a between-measurement coefficient variable of well below 10% and a sensitivity of the OCT technique to detect changes in the range of 5–10 μm. Clinical studies have determined that dental erosion varies considerably between the upper and lower arches, individual teeth, and, indeed, specific tooth surfaces of those teeth (36). Enamel measurements averaged across four specific locations per tooth show considerable variability by location. Because measurements are not always available for the same teeth for all patients, and because susceptibility to acid attack and erosive experience differ so extensively between individual teeth in the same patient, analysis of data was by tooth rather than averaged across all teeth per patient. With a sample size of 30 patients for whom measurements were obtainable on an average of 12 teeth per patient (360 teeth), the study provided greater than 80% power to detect a difference between treatment groups in change in enamel thickness of approximately 0.4 s.d. using a two-group *t* -test with 5% significance level. A per protocol approach was used for the statistical analysis.

The predefined primary efficacy variable was the change in thickness of the enamel at four specific landmark locations for each tooth, measured before and after treatment. Secondary variables for analysis were the following: the optical reflectance changes at the enamel surface and at depth intervals of 1 pixel down to the enamel–dentin junction, measured at the four standardized locations. Optical data were evaluated using a repeated measures analysis of variance with one repeated factor (before-after) and two grouping factors (treatment group placebo or esomeprazole, and tooth). For enamel measurements, data from the site of maximum enamel loss for each tooth were averaged across the four standardized locations on each tooth for each patient to derive before and after average values per tooth. For the optical data, mean before and after treatment values for the four standardized sites per tooth were compared between active and placebo treatment groups. Data were compared using repeated measures analysis of variance with one within-group factor (before vs. after) and two between-group factors (tooth and treatment). After adjusting for any between-subject differences with respect to tooth, the significance of the interaction factor for time by treatment (*F* -test with 1 d.f) provides a test for differences over time between the drug and placebo groups.

Cantonal Ethics Committee approval was gained for this study (8 February 2008), which was performed in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements. The study was registered in www.clinicaltrials.gov (number NCT 00564330).

Results

Participant flow and follow-up

Patient characteristics are shown in Table 2. Of the 41 successive patients contacted, eight declined participation due to personal reasons. One patient was discontinued from the esomeprazole group due to poor compliance. There were no significant differences in characteristics between the two treatment groups. Before vs. after treatment reflux data were not analyzed, as this was not predefined due to the inadequate sample size for this comparison. Of the total of 42 tablets per patient, on average 1 tablet was missed or taken late in both treatment groups. No significant adverse events were registered during the study.

Of the total 368 teeth analyzed (170 esomeprazole and 198 placebo treated), data from 8 teeth were not included in the analysis due to inaccurate relocalization of the probe at the second imaging event, so that before and after treatment images and data could not be meaningfully compared.

Enamel thickness

Table 3 shows before and after study enamel thickness for both groups, as well as the change during treatment. The mean±s.e.m. decrease in enamel thickness of all teeth at the site of maximum enamel loss after 3 weeks was 7.2±0.16 μm with esomeprazole and 15.3±0.17 μm with placebo ($P = 0.013$), representing a loss of approximately 0.3 and 0.8% of total enamel thickness, respectively. Enamel loss is shown in an OCT tooth scan of a typical patient before and after placebo treatment in Figure 1.

Optical data

In the pre-study OCT images of teeth (Figure 2), there is at first an intense backscattered signal at the air–enamel interface, with the rest of the signal becoming progressively less intense with increasing depth into the sample. Pre-study images are similar for all teeth in both groups with regard to the gradient of signal intensity and localization. By the end of the study, small but obvious differences can be seen between the two treatment groups. Post-study, in the placebo group, there is a relatively similar intense reflection rise at the initial interface. However, there is considerably more intense signal backscattering with depth beyond the surface (Figure 2a). With placebo the change in optical reflectivity to a depth of 25 μm after treatment was + 2.059 ± 0.534 dB. In the esomeprazole group post-study there is again a relatively similar intense reflection rise at the initial air–enamel interface, but there is considerably reduced signal backscattering with depth beyond the surface compared with pre-study (Figure 2b). The change in optical reflectivity to a depth of 25 μm after treatment was − 1.1220 ± 0.769 dB, differing significantly from that of the placebo group ($P = 0.012$).

Discussion

Significant differences in tooth enamel thickness and optical reflectance were seen with *in vivo* OCT imaging after 3 weeks of double-blind treatment with placebo or a potent acid blocker, esomeprazole, in this first study of patients with GERD-related dental erosions. Progressive enamel tissue loss and demineralization, as shown by optical reflectance

changes, were seen after only 3 weeks in the placebo group. These changes were prevented to a significant degree by a twice-daily dose of esomeprazole (20 mg), with evidence of remineralization shown by decreased optical reflectance at a depth of 25 μm, as well as significantly slowed loss of enamel.

Increased signal intensity in OCT images of teeth correlated with demineralization in previous *ex vivo* studies simulating incipient dental decay (37). The process of demineralization causes mineral loss and a multitude of pores of different sizes (38,39). When light travels through such a complex structure, in addition to scattering by intact enamel rods, it interacts with the pores caused by demineralization, resulting in greater light intensity being sent toward the detection system when compared with the signal obtained in the healthy specimens. Two processes contribute to this phenomenon. First, back reflections occurring at the pore–enamel interfaces due to abrupt changes of the optical refractive index and, second, an effective reduction in scattering when light is traveling virtually without being deviated through the space inside the pores (33,40). This effect ensures that light coming from deeper regions within the sample reaches the OCT detection system. The final result of these two processes amounts to more OCT signal being recorded as arising from deeper within the demineralized enamel matrix compared with a signal that probes sound enamel and does not penetrate too deep into the sample (38,40,41). Previous studies comparing dental OCT images of healthy and demineralized teeth with their histology and Raman spectroscopy confirmed the correlation between increased OCT signal intensity and demineralization (40,41).

Conversely, in the esomeprazole group, demineralization was largely prevented, as indicated by the decreased backscattering signal, and the acid-blocking effects of esomeprazole may even have exerted a beneficial effect on the teeth through a mild remineralization of the teeth as compared with their initial status at the beginning of the study. This hypothesis is reasonable based on the fact that all patients in the study were affected by GERD, and therefore their teeth had some degree of demineralization at the study onset. Saliva is known to promote remineralization of dental hard tissues (42). No direct effect of proton pump inhibitors on dental mineralization has been reported to the best of our knowledge.

Overall, teeth from patients in the esomeprazole group also showed some loss of enamel, although significantly less than the placebo group. This may be due to incomplete acid control with a dose of 20 mg twice daily in a proportion of patients. Oral pH studies during esomeprazole dosing have not been reported. We chose split dosing with 20 mg b.i.d. in this first study, as control of gastric, especially nocturnal pH is improved with 20 mg b.i.d. compared with 40 mg in healthy volunteers (19,43,44). Nocturnal acid control is particularly difficult to achieve with proton pump inhibitors, and many of the GERD patients with dental erosions show protracted acid reflux during the night.

Enamel thickness varies widely between individuals and locations, complicating comparisons between studies. It can be assumed the enamel thickness in our patients with chronic GERD verified by pH-metry was already diminished before the start of the study. The mean enamel loss of 15.3 μm over 3 weeks in controls in the current study was approximately double the annual loss of 7.4 μm seen in controls in a study assessing patients

with unexplained palatal dental erosions, who had a median annual loss of 73 μm of enamel (45).

At present, quantification of dental tissue loss is performed by visual scoring using standardized scales. Current indices are subdivided into 2–5 degrees, rendering assessment of small changes impossible. More degrees will lead to lower reproducibility. An objective and sensitive method, such as the OCT presented here, would allow the early detection of the loss of dental hard tissue and the implementation of timely preventive measures.

Using the fiberoptic OCT probe with the stent made of impression material proved to be relatively unproblematic, with patients tolerating the process well. For most patients and teeth, accurate probe relocalization was achieved very successfully. However, in a few teeth, positioned at an inaccessible angle, especially toward the back of the mouth, access with the OCT probe was difficult or even impossible. It is in these teeth that colocalization at the two imaging events was not sufficiently accurate to permit a meaningful comparison of before treatment vs. after treatment data. Imaging the lingual surfaces of some anterior teeth was not possible due to inaccessibility by the stiff probe. Further technical developments are required to allow more complete imaging access.

Enamel thickness measurement using OCT and a superimposed measurement grid was quick and unproblematic. Imaging depth was more than adequate to measure full enamel thickness, and anatomical landmarks at the enamel–dentin junction served well as accurate baseline marker points. Previous studies have demonstrated excellent reproducibility of OCT imaging for multiple OCT imaging events and measurements (41,42,46–48).

We opted to compare data by teeth rather than by patient due to the significant within-patient variability and the variable number of teeth available per patient. Within-patient variability was minimized by taking an average over all teeth per patient. Re-analysis of the data by patient, using each patient's mean value for enamel thickness, revealed a consistent magnitude of difference in enamel thickness between placebo- and esomeprazole-treated groups, with both forms of analysis yielding some statistical significance for each comparison.

Besides the above-mentioned limitations, it should be pointed out that pH-metry for quantification of gastroesophageal reflux was performed at the classic location of 5 cm above the lower esophageal sphincter, which will not accurately reflect the actual reflux reaching the dental tissue, although a significant but not very tight correlation has been reported by Bartlett *et al*. (11). At the time of the study, pH-impedance measurements with additional information on weakly acidic as well as proximal esophageal reflux were not available in our clinic. This technique would have added an additional useful dimension to the results and will be used in subsequent larger studies. Protracted measurement of oral reflux is being developed, but is not yet available for clinical use. In addition, no dose–response study was performed with esomeprazole to ascertain the most effective and protective dose. The duration of only 3 week's treatment was opted for because of ethical concerns with more protracted dosing with placebo, namely progressive, irreversible dental damage. Other control groups will have to be used in longer term studies. Most of the

patients in this study had mildly symptomatic GERD, as they presented with a primary complaint of dental erosions and not GERD symptoms. It should be emphasized that all patients were screened for dietary and non-GERD-related causes of dental erosions by the dental clinic before referral for GERD evaluation. Of the total of over 300 such patients seen by us through this referral route in the last few years over 90% had documented, abnormally increased reflux. This study was not designed and is far too small to provide guidelines on the clinical management of these patients. However, given our current experience we would currently recommend investigation of GERD in patients with dental erosions even without any symptoms of GERD. As previously stated, no currently published data yet exists to support this opinion.

In conclusion, OCT was able to show the loss of dental tissue in GERD after a period of only 3 weeks and a significant reduction of this loss using esomeprazole. Application of the above data to a broad spectrum of GERD patients with dental erosions should await confirmation of our data in a larger and more extensive study.

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Study Highlights

What is Current Knowledge

- Dental erosions are increasingly discovered in gastroesophageal reflux disease (GERD) patients.
- Patients with dental erosions may have undiscovered GERD.

What is New Here

- Dental enamel erosion and demineralization can be reliably quantified using optical coherence tomography.
- Significant dental enamel loss is seen within 3 weeks of observation without treatment.
- Esomeprazole partly prevented this dental enamel loss.

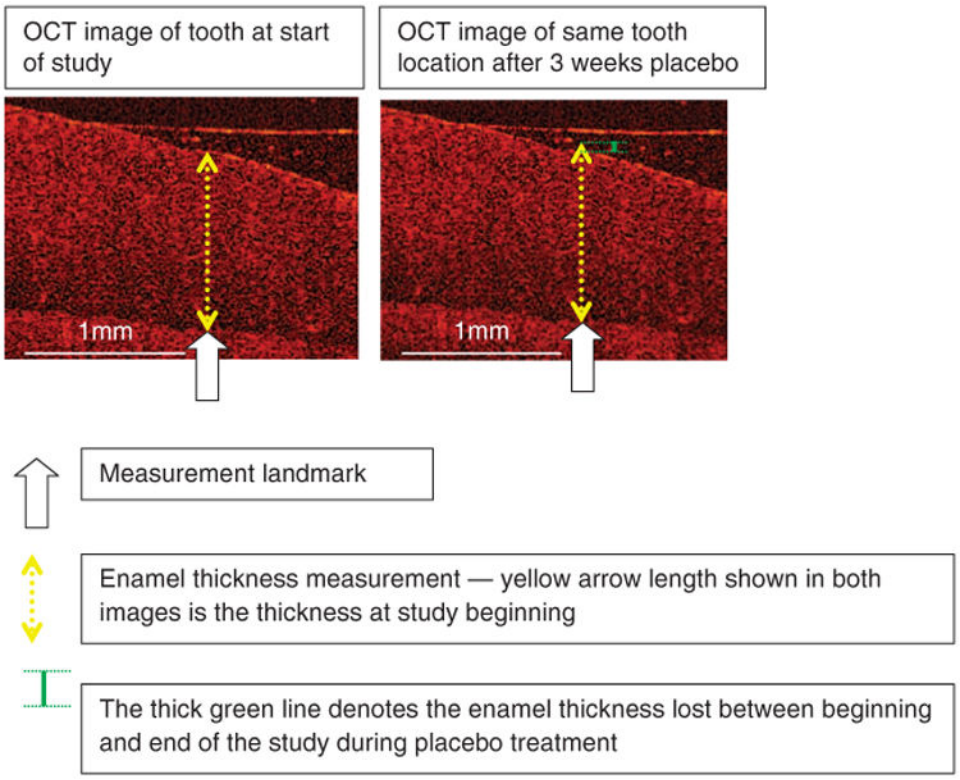

Figure 1.

Typical *in vivo* optical coherence tomography (OCT) images of the same tooth before and after 3-week treatment with placebo showing pre-study enamel thickness and post-study enamel loss (green lines).

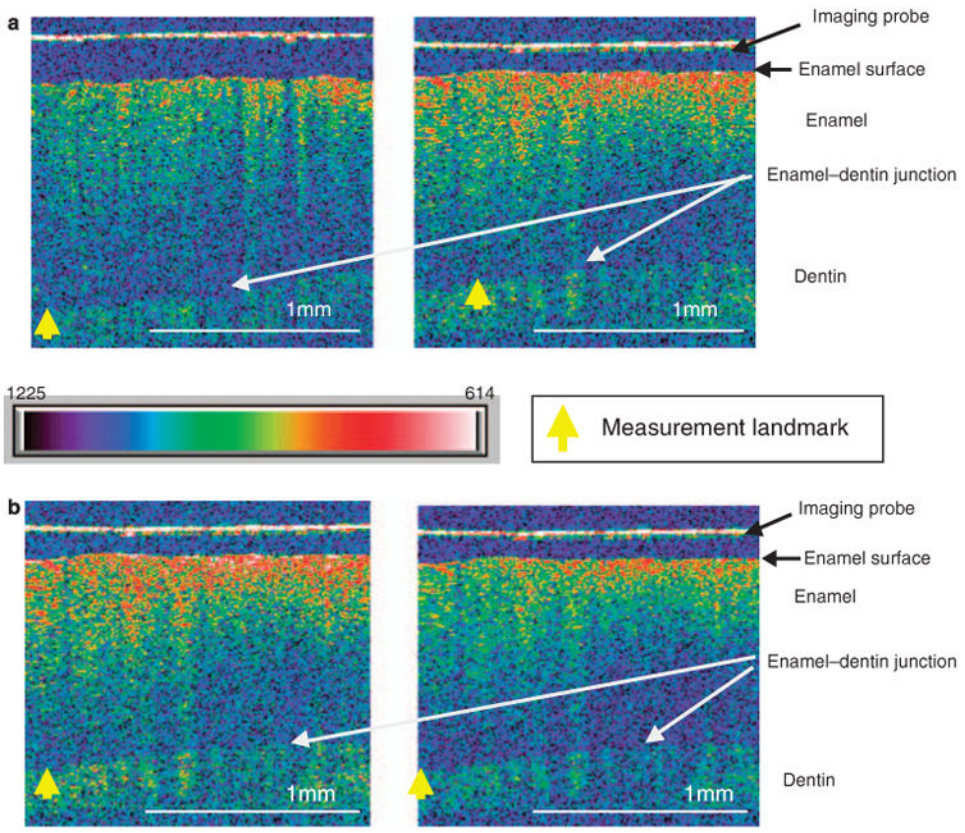

Figure 2.

(**a**) *In vivo* optical coherence tomography (OCT) images with pseudo-color superimposition of the same tooth before and after 3-week treatment with placebo. The optical signal near the tooth surface has increased as shown by the greater preponderance of green vs. blue. (**b**) *In vivo* OCT images with pseudo-color superimposition of the same tooth before and after 3-week treatment with esomeprazole 20 mg b.i.d. The optical signal near the tooth surface has decreased as shown by the reduced preponderance of red vs. green.

Table 1
Lussi scores for dental assessment of erosion (ref. (34))

Score	Surface	Criteria
	Facial	
0		No erosion. Surface with a smooth, silky-glazed appearance, absence of developmental ridges possible.
1		Loss of surface enamel. Intact enamel found cervical to the lesion. Concavity in enamel, the width of which clearly exceeds its depth, thus distinguishing it from toothbrush abrasion. Undulating borders of the lesions are possible. Dentin is not involved.
2		Involvement of dentin for less than one-half of the tooth surface.
3		Involvement of dentin for more than one-half of the tooth surface.
	Occlusal/oral	
0		No erosion. Surface with a smooth, silky-glazed appearance. Absence of developmental ridges possible.
1		Slight erosion, rounded cusps, edges of restorations rising above the level of adjacent tooth surface, grooves on occlusal aspects. Loss of surface enamel. Dentin is not involved.
2		Severe erosion, more pronounced signs than grade 1. Dentin is involved.

Table 2

Patient characteristics

	Esomeprazole, *n* =14	**Placebo, *n* =15**
Age[a]	33.2 ± 9	31.5 ± 11
Gender (male/female)	10/4	12/3
Endoscopic finding		
Hiatal hernia (yes/no)	8/6	2/15
Esophagitis (yes/no)	3/11	4/11
GERD symptoms (>2/week), *n* patients	1	2
Reflux disease questionnaire score before/after 3-week treatment (max. score = 60) (35)[a]	3.2 ± 2/3.8 ± 3	5.0 ± 4/5.4 ± 4
24 h esophageal pH-metry: % time pH < 4[a]	23.3 ± 14	19.4 ± 19
Dental erosions scores (*n* teeth with Lussi score >1) (34)[a]	7.4 ± 5	8.4 ± 6

[a]Mean ± s.d.

Table 3
Pre- and post-treatment enamel thickness and optical reflectance intensity

	Pre-treatment	Post-treatment	Change
	Mean measured enamel thickness at probe location ± s.e.m.		
Esomeprazole, *n* = 167 teeth	2142.6 μm ± 0.16	2135.4 μm ± 0.16	7.2 μm ± 0.16*
Placebo, *n* = 193 teeth	2215.9 μm ± 0.17	2200.6 μm ± 0.17	15.3 μm ± 0.18*
	Mean measured optical intensity at probe location ± s.e.m.		
Esomeprazole, *n* = 167 teeth	55.8879 dB ± 0.7690	54.7659 dB ± 0.7600	−1.1220 dB ± 0.7691#
Placebo, *n* = 193 teeth	52.2864 dB ± 0.5404	54.3454 dB ± 0.5339	+2.0590 dB ± 0.5329#

*$P = 0.013$;

#$P = 0.012$.