

A placebo-controlled multi-centred evaluation of an anaesthetic gel (Oraqix[®]) for periodontal therapy

D. Donaldson^{1*}, S. C. Gelskey²,
R. G. Landry³, D. C. Matthews⁴ and
H. S. Sandhu⁵

¹Faculty of Dentistry, The University of British Columbia; ²Faculty of Dentistry, The University of Manitoba; ³Faculty of Dentistry, Université Laval; ⁴Faculty of Dentistry, Dalhousie University; ⁵Faculty of Dentistry, The University of Western Ontario, Canada

Donaldson D, Gelskey SC, Landry RG, Matthews DC, Sandhu HS: A placebo-controlled multi-centred evaluation of an anaesthetic gel (Oraqix[®]) for periodontal therapy. *J Clin Periodontol* 2003; 30: 171–175. © Blackwell Munksgaard 2003.

Abstract

Aims: Six Canadian dental schools investigated the ability of a thermosetting gel containing 25 mg/g prilocaine and 25 mg/g lidocaine as active agents to produce analgesia in periodontal pockets utilizing a randomized, double-blind, placebo-controlled study.

Materials and Methods: The study consisted of 130 patients, each of whom received the active or placebo gel in periodontal pockets in one quadrant of the mouth for 30 s prior to periodontal debridement (scaling and root planing). Pain was measured using both a 100-mm Visual Analogue Scale (VAS) and a Verbal Rating Scale (VRS).

Results: The median VAS pain score for the patients treated with the anaesthetic gel was 5 mm (range 0–85 mm) as opposed to 13 mm (range 0–79 mm) in the placebo-treated patients ($P = 0.015$). There was no significant difference in the percentage of patients reporting no or mild pain (78% and 76% for the anaesthetic gel and placebo, respectively). No significant differences were seen in patient demographics, or *mandible versus maxilla*.

Conclusions: The VAS pain scores showed that the anaesthetic gel 5% was statistically more effective than the placebo in reducing pain during periodontal debridement.

Key words: topical anaesthesia; periodontal treatment

Accepted for publication 30 January 2002

It is estimated that 30–40% of the population suffers from periodontal disease (Brown et al. 1990). To eliminate or control the disease and arrest further periodontal tissue destruction, periodontal pockets require repeated subgingival mechanical debridement. A large proportion of scaling and periodontal debridement procedures performed involve nerve block or infiltration anaesthesia. Injection anaesthesia may be carried out alone or in conjunction with topical anaesthesia; however, the pain of needle insertion, duration of action and inconvenience of soft tissue anaesthesia limit patient acceptance. Efficacy, uncontrolled spreading and undesirable taste limit the use of topical agents (Milgrom et al. 1997). There is therefore a need for a fast acting anaesthetic that is simple to apply and painless. The purpose of this

randomized, parallel group, double-blind study was to determine the anaesthetic efficacy of anaesthetic gel (Oraqix[®]) compared to a placebo for *non-surgical* periodontal debridement.

Materials and methods

Oraqix[®] contains the active ingredients lidocaine 25 mg/g and prilocaine 25 mg/g. It also contains hydrochloric acid, purified water and a thermosetting agent, which causes the solution to pass from the liquid state at room temperature to a gel state at the temperature of the oral cavity. This allows the active ingredient to be held in place for a sufficient period of time to be effective.

This was a randomized, parallel group, double-blind study using the anaesthetic gel and a placebo gel.

Volunteer subjects were recruited from six dental schools. Participants were required to present with a quadrant with a minimum of five teeth that had not received periodontal debridement in the last 12 months. At least three of the teeth in the selected quadrant were required to have one or more periodontal pockets with a depth of 5 mm or greater. Subjects were 18 years of age or older and able to understand and complete a Visual Analogue Scale (VAS) and a Verbal Rating Scale (VRS). Subjects signed an informed consent. The study was approved by local ethics review boards and performed in agreement with the declaration of Helsinki.

Participants were screened and then randomized into treatment groups. The operator, patient and assistant at each

centre were blinded to the type of gel assigned. Hypersensitive teeth were identified by isolating the teeth with a gauze square and using a 2-s stream of compressed air. Pocket depths and any bleeding or purulent exudates on probing were assessed at six surfaces of all teeth at baseline.

The test quadrant was isolated with cotton rolls. The active or placebo was administered within a 30 s time period at the gingival margin around the most posterior and the adjacent gingival margin in the selected quadrant using a standard dental cartridge system with a blunt-ended, needle-shaped applicator (23 gauge, 0.6 mm). The gel was then placed into the periodontal pocket. The gel was left in the periodontal pocket for between 30 s and 2 min whereupon periodontal debridement commenced utilizing conventional, universal and area-specific cures. The procedure continued anteriorly to the next tooth until the quadrant was completed.

If there was an interruption due to pain, re-application of the gel occurred directly into the pockets of the same tooth and debridement resumed 30 s later. If the debridement, after re-application, was not interrupted due to pain, the procedure was continued in a sequential fashion to complete the quadrant. However, if the debridement was still painful after re-application, no further application of the gel was allowed and the subject was classified as requiring rescue anaesthetics, which was an efficacy parameter in the study.

The subject's overall pain from debridement was assessed immediately after completion of periodontal debridement using a 100-mm horizontal, ungraded VAS, with the left end-point marked 'no pain' and the right end-point marked 'worst pain imaginable'. To ensure that subjects understood the use of the VAS, a pilot VAS assessment was performed prior to the study.

Pain from debridement was also assessed using a five-point VRS of no pain, mild pain, moderate pain, severe pain and very severe pain. Assessment of the VAS pain score was made prior to the VRS pain scores in order to avoid any influence of an already selected verbal expression.

At the end of the debridement procedure, even if stopped prematurely, all patients were asked to rate their overall pain perception on the VAS and the VRS. If a rescue anaesthetic had to be given, the pain assessments were

Table 1. Age by treatment group and centre

Centre	Anaesthetic gel		Placebo gel	
	<i>n</i>	Age (years) median (range)	<i>n</i>	Age (years) median (range)
1	12	38 (23–75)	13	40 (23–61)
2	16	54 (35–57)	17	45 (34–69)
3	8	45 (29–67)	8	50 (31–67)
4	15	44 (28–73)	15	39 (32–80)
5	6	55 (43–66)	8	48 (37–63)
6	6	52 (38–66)	6	65 (52–79)
All	63	47 (23–75)	67	45 (23–80)

made before the alternate anaesthetic was administered. Possible adverse events were monitored throughout the treatment period and at the follow-up telephone call 24–48 h post-treatment.

Statistical analysis

The Spearman rank correlation coefficient statistic was used for the overall VAS versus VRS. For the VAS and VRS pain score, the Stratified Wilcoxon rank-sum test, stratified by centre, was used. The 95% confidence interval and Hodges-Lehmann point estimate (HL-estimate) of the difference between treatments was calculated. The test was two-sided with a statistical significance if the *P*-value was ≤ 0.05 . The minimum clinically relevant difference in the primary efficacy parameter (overall VAS score) was predefined as 15 mm. Assuming a standard deviation (SD) of 25 mm, a sample size of 59 evaluable patients per group was required in order to detect a statistically significant difference with a probability (power) of at least 90%. In these power considerations, a simple unstratified two-sample *t*-test with *P* = 0.05 was used under assumptions of normality.

Results

A total of 130 eligible subjects were recruited and randomized to one of the two treatment groups: 63 to the active group and 67 to the placebo group. All 130 subjects completed the study and were valid for statistical analyses.

Sex and race distribution, and periodontal disease involvement were similar between treatment groups (Tables 1 and 2). The median dose of active and placebo gel administered was three-quarters of a cartridge or 1.3 g per patient or 0.2 g per tooth.

The median VAS pain score was 5 mm in the active group and 13 mm in the placebo group. In the pooled analysis, stratifying by centre, the HL-estimate of the treatment difference was 4 mm (*P* = 0.015). In the placebo group there was a large centre variation in the VAS pain score, with the median scores ranging from 6.0 to 38.0 mm. In the Dental Gel 5% group the variation was smaller, with medians ranging from 0 to 19 mm. In the two centres with median VAS pain scores of more than 30 mm in the placebo group, the differences between treatment groups were clinically significant: 16.5 and 21.5 mm (HL-estimate), respectively (Table 3).

From the VRS, 78% of the subjects in the test group reported no or mild pain while in the placebo group the corresponding figure was 76%. In both test and placebo groups, 5% of patients reported having severe pain. The overall VRS pain score was not statistically significantly different between the two groups (*P* = 0.23).

There was a statistically significant correlation between the overall VAS and VRS pain scores with a correlation coefficient value of 0.79 (*P* < 0.0005).

There was no statistical differences (*P* = 0.75) between the VAS or VRS scores for the mandible (*n* = 47) and the maxilla (*n* = 83).

In the test group, four out of 63 patients (6%) needed rescue anaesthetic whereas in the placebo group the corresponding figure was seven out of 67 (10%), such low numbers that statistical tests were not performed.

Six patients in the active group and five patients in the placebo group reported adverse events, the majority being in the oral cavity and included numbness, soreness, discomfort and pruritis. None of the adverse events were of major clinical significance. They were all transient with no residual effect.

Table 2. Dental assessment by treatment group and centre. For each patient the mean pocket depth (6 surfaces per tooth), proportion of bleeding pockets and proportion of hypersensitive teeth was calculated. It is the medians and ranges of these individual means and proportions that are presented in this table

Group	Centre	<i>n</i>	Patients' mean pocket depth (mm) median (range)	Patients' proportion of bleeding pockets of median (range)	Patients' proportion hypersensitive teeth median (range)
Anaesthetic gel	1	12	3.6 (3.2–4.3)	0.8 (0.5–1.0)	0.4 (0.0–0.7)
	2	16	3.3 (3.0–4.0)	0.3 (0.2–0.5)	0.0 (0.0–0.6)
	3	8	3.3 (2.6–3.8)	0.3 (0.3–0.6)	0.0 (0.0–0.2)
	4	15	3.5 (2.6–5.8)	0.6 (0.2–1.0)	0.0 (0.0–0.0)
	5	6	3.3 (2.8–4.3)	0.2 (0.0–0.9)	0.2 (0.0–0.8)
	6	6	3.5 (3.2–5.0)	0.4 (0.2–0.7)	0.2 (0.0–0.6)
	All	63	3.5 (2.6–5.8)	0.4 (0.0–1.0)	0.0 (0.0–0.8)
Placebo gel	1	13	3.7 (3.2–5.0)	0.7 (0.3–1.0)	0.3 (0.0–0.8)
	2	17	3.4 (2.9–4.6)	0.2 (0.1–0.5)	0.0 (0.0–0.3)
	3	8	3.8 (3.4–4.5)	0.7 (0.0–0.9)	0.4 (0.0–1.0)
	4	15	3.5 (2.8–5.3)	0.6 (0.3–1.0)	0.0 (0.0–0.0)
	5	8	3.3 (3.1–3.7)	0.2 (0.1–0.6)	0.0 (0.0–0.6)
	6	6	3.2 (3.0–3.9)	0.4 (0.3–0.6)	0.1 (0.0–0.7)
	All	67	3.5 (2.8–5.3)	0.5 (0.0–1.0)	0.0 (0.0–1.0)

Table 3. Pain scores: overall VAS (mm) during SRP, by treatment group and centre

Centre	<i>n</i>	Overall VAS (mm) median (range)		Treatment difference (placebo – anaesthetic gel) Hodges-Lehmann point estimate
		Anaesthetic gel	Placebo gel	
1	25	2 (0–60)	38 (0–68)	22 mm
2	33	5 (0–30)	10 (0–40)	2 mm
3	16	12 (3–85)	32 (5–79)	16 mm
4	30	10 (0–53)	6 (0–44)	0 mm
5	14	19 (0–53)	8 (0–42)	– 6 mm
6	12	0 (0–2)	14 (1–35)	14 mm
All	130	5 (0–85)	13 (0–79)	4 mm (CI 0–10 mm) <i>P</i> = 0.015

CI = 95% confidence interval.

Discussion

The primary objective of this multi-centre study was to determine the local anaesthetic efficacy of the test gel Orajix[®] compared to a placebo gel by assessing the overall pain associated with periodontal debridement using a VAS and VRS. A parallel group study design was selected rather than a cross-over design to avoid the possibility of a carry-over effect caused by the subjects' perception of pain from the previous treatment period. In addition, the parallel group design contributed to subject blinding with regard to a possible difference in taste or gel consistency between the active and placebo gels.

The primary means of determining gel efficacy was the measurement of

treatment-associated pain. The use of the VAS for scoring pain has been validated in a variety of studies for different conditions including rheumatoid arthritis (Scott & Huskisson 1976) and temporomandibular disorder pain (Le Resche et al. 1988). The reliability of the VAS and VRS has been demonstrated previously using the test/re-test method for repeated measures of subjective sensations (Luria 1975). The reliability of the VAS was shown to be excellent (kappa 0.82) while that of the VRS was good (kappa 0.59) (Fleiss 1981, Kelsey et al. 1986, Le Resche et al. 1988).

Thus the VAS and the VRS represent appropriate methods for measuring subjective pain. However, the subject nature of VAS and VRS may over or

underestimate the efficacy of the test gel.

The placebo gel produced VAS pain scores which were low. As a result, it was difficult to demonstrate clinically relevant lower values in the test group. However, in centres where the placebo-treated patients reported high VAS pain scores (median > 30 mm), the test gel reduced the pain by at least 50% compared to the placebo gel. This may be related to the average pressure habitually exerted by the operator during SRP, which has been shown to vary (Zappa et al. 1991).

In some centres, the placebo group had lower VAS pain scores than expected. It was the impression of the investigators/clinicians that the majority of subjects recruited by these centres were periodontal maintenance patients who were familiar with the debridement procedure, whereas the other centres had recruited treatment-naïve subjects, that is, subjects who had never undergone the procedure. This difference in subject type along with centre differences in operator technique may offer additional reasons for observed differences in pain scores and an underestimation of gel efficacy compared to the placebo gel.

An exploratory statistical analysis indicated a trend towards higher VAS scores in the placebo group when the pocket depths were deeper and the proportion of bleeding pockets were higher (Figs 1,2 and 3). No such trend was seen in the test group. This may suggest that the test gel has a more pronounced effect in reducing pain associated with debridement in advanced cases of periodontal disease, while it may be less beneficial for patients with milder periodontitis.

While there was a statistically significant treatment difference in overall VAS pain scores, the VRS pain scores did not reach statistical significance. This may seem surprising, but one needs to remember that the study was powered for the primary efficacy variable (overall VAS), which is also a more sensitive method.

The gel was left in the periodontal pockets for only 30 s to 2 min before commencing with debridement, which could have reduced the efficacy of the gel if it had not reached its full potential. However, previous studies have shown that the onset of anaesthesia using Dental Gel was within 30 s to 2 min (Friskopp et al. 2001.)

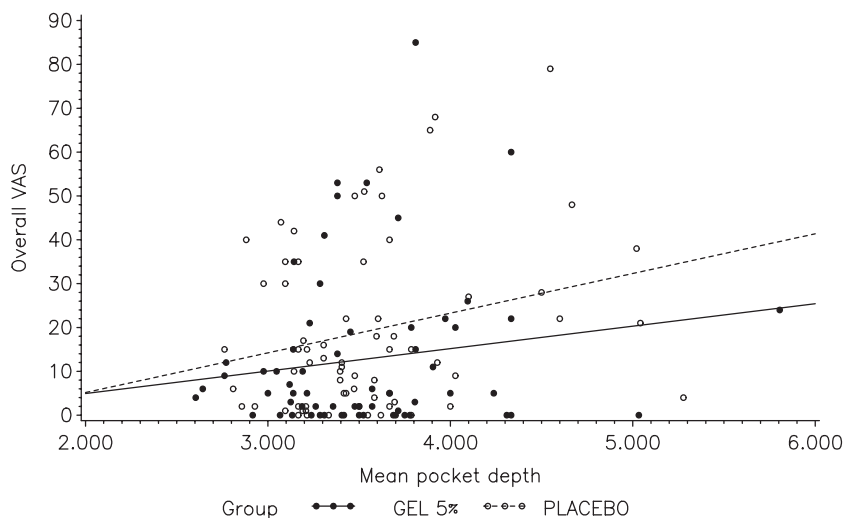


Fig. 1. Influence of the patient's mean pocket depths on the overall VAS pain score. Scatter plot with fitted linear regression lines.

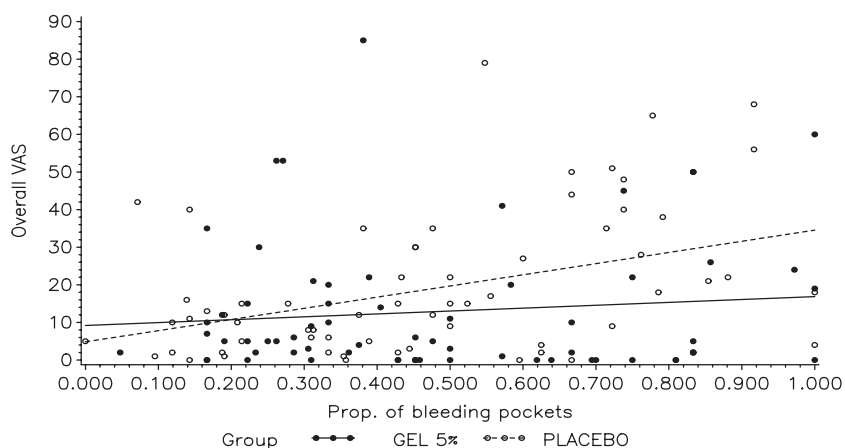


Fig. 2. Influence of the patient's proportion of bleeding pockets on the overall VAS pain score. Scatter plot with fitted linear regression lines.

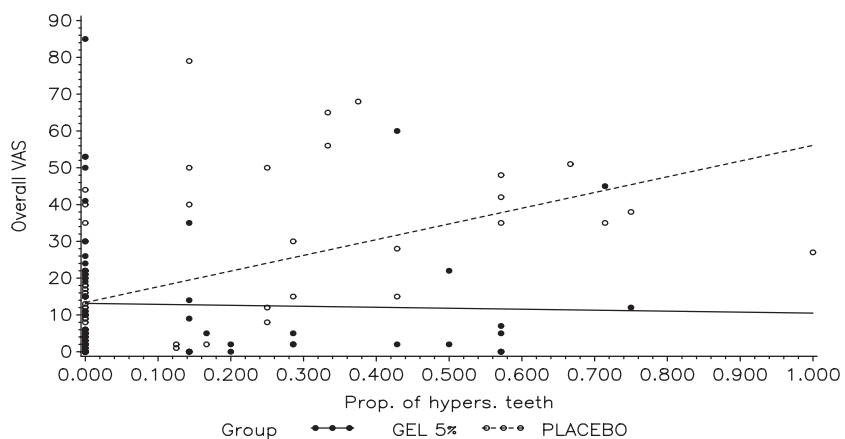


Fig. 3. Influence of the patient's proportion of hypersensitive teeth on the overall VAS pain score. Scatter plot with fitted linear regression lines.

A predecessor to Oraqix[®], a 5% eutectic mixture of local anaesthetics (EMLA cream) consisting of 2.5% lidocaine and 2.5% prilocaine, has been suggested to produce some degree of pulpal anaesthesia (Vickers & Punnia-Moorthy 1993). The residual amount of pain experienced by subjects in this study was most likely due to impulses arising from the tooth pulp. The current study did not control for the possible confounding effect of dentinal hypersensitivity, although it did assess its presence at baseline.

In this study, only a few patients reported adverse events. It is important to note, however, that small gingival effects may have been missed since adverse events were only followed-up by a telephonic interview after 24–48 h.

Previous studies have demonstrated that approximately two-thirds of patients undergoing periodontal debridement considering the procedure painful and unpleasant (Svensson et al. 1994). A local anaesthetic is frequently administered to alleviate patient discomfort. However, current anaesthesia techniques including the nerve block and infiltration are associated with limitation: (1) pain associated with needle insertion and solution injection (Milgrom et al. 1997); (2) lengthy duration of anaesthesia; and (3) unnecessary anaesthesia in surrounding tissues. It would be desirable if an effective, fast-acting topical anaesthesia preparation would be available.

Conclusion

Lidocaine, prilocaine anaesthetic gel 5% is a product which is well-tolerated for local anaesthesia of the periodontium. In the study population, the active gel was overall statistically significantly more effective than the placebo and clinically effective in reducing pain associated with periodontal debridement for those patients who perceive the procedure to be painful. The results of this study suggest that lidocaine, prilocaine gel 5% may offer an alternative to injection anaesthesia. However, further studies are required to confirm its true efficacy.

Acknowledgements

The authors are grateful to Mrs Ingrid Ellis for her editorial assistance in the final preparation of the manuscript. This study was supported by AstraZeneca Pain Control, Sweden.

Zusammenfassung

Placebo-kontrollierte Multicenter-Untersuchung eines für die Parodontaltherapie bestimmten Anästhesie-Gels (Oraqix[®])

An 6 Kanadischen Universitätszahnkliniken wurde ein thermisch sich verfestigendes Anästhesie-Gel in einer randomisierten Placebo-kontrollierten Doppel-Blind-Studie hinsichtlich seiner schmerzlindernden Wirkung untersucht. Als aktive Wirkstoffe enthält das Gel 25 mg/g Prilocain und 25 mg/g Lidocain. In die Studie wurden 130 Patienten aufgenommen, welche in die Taschen eines Quadranten des Gebisses 30 Sekunden vor dem parodontalen Debridement (Scaling und Wurzelglättung) entweder das aktive oder das Placebo-Gel bekamen. Der Schmerz wurde durch eine 100-mm Visuelle Analog-Skala (VAS) und eine Verbale Rating-Skala (VRS) bestimmt. Der mediane VAS-Schmerzwert betrug für Patienten, die mit Anästhesie-Gel behandelt wurden, 5 mm (Schwankungsbreite 0-85 mm) im Gegensatz zu 13 mm (Schwankungsbreite 0-79 mm) für die mit Placebo behandelten Patienten ($p = 0,015$). Es gab keinen signifikanten Unterschied zwischen dem Prozentsatz der Patienten, welchen über keinen oder nur leichten Schmerz berichteten (78% und 76% für das Anästhesie-Gel bzw. das Placebo). Es wurden keine signifikanten Unterschiede bei den demographischen Daten der Patienten oder hinsichtlich der Wirkung im Ober- versus Unterkiefer beobachtet. Die VAS-Schmerzwerte zeigten, dass das 5%ige-Anästhesie-Gel bei der Schmerzreduktion während des parodontalen Debridements statistisch effektiver ist als das Placebo.

Résumé

Une évaluation de plusieurs centres avec placebo d'un gel anesthésique (Oraqix[®]) pour le traitement des parodontopathies

Six écoles dentaires canadiennes ont fait une étude sur l'abilité d'un gel thermodurcissable contenant comme agents actifs 25 mg/g de

prilocaine et 25 mg/g de lidocaine à produire une analgésie dans une poche parodontale par le moyen d'une étude au hasard et à l'aveuglette avec placebo.

Les 130 malades étudiés ont tous reçu soit le gel actif ou le gel placebo dans une poche parodontale d'un quadrant de leur bouche pendant 30 seconde avant un débridement parodontal (détartrage et curetage de la surface de la racine). Leur réaction à la douleur fut mesurée en utilisant une Échelle Analogue Visuelle (VAS) de 100-mm et une Échelle de l'Estimation Verbale (VRS).

Les résultats médians de la douleur sur l'échelle VAS pour les malades traités avec le gel anesthésique était de 5 mm (sur une gamme de 0 à 85mm) et de 13mm (sur une gamme de 0 à 79mm) pour les malades traités avec le gel placebo ($P = 0.015$).

Il n'y avait pas de différence notable dans le pourcentage des malades ressentant peu ou pas de douleur (78% pour le gel anesthésique et 76% pour le placebo). Il n'y avait pas de différence marquée dans la démographie des malades ou entre le maxillaire inférieur et supérieur.

Les résultats du VAS ont démontré que le gel anesthésique à 5% était statistiquement plus efficace que le placebo pour réduire la douleur lors d'un débridement parodontal.

References

- Brown, L. J., Oliver, R. C. & Loe, H. (1990) Evaluating periodontal status of U.S. employed adults. *Journal of American Dental Association* **121**, 226–232.
- Fleiss, J. L. (1981) *Statistical methods for rates and proportions*, 2nd edition., Toronto: John Wiley.
- Friskopp, J., Nilsson, M. & Isacson, G. (2001) The anesthetic onset and duration of a new lidocaine/prilocaine gel intra-pocket anesthetic (Oraqix) for periodontal scaling/root planing. *J* **28**, 453–458.

- Kelsey, J. L., Thompson, W. D. & Evans, A. S. (1986) *Methods in observational epidemiology: monographs in epidemiology and biostatistics*, pp. 3–366. NY: Oxford University Press.
- Le Resche, L., Burgess, J. & Dworkin, S. F. (1988) Reliability of visual analog and verbal descriptor scales for "objective" measurement of temporomandibular disorder pain. *Journal of Dental Research* **67**, 33–36.
- Luria, R. E. (1975) The validity and reliability of the visual analogue mood scale. *Journal of Psychiatric Research* **12**, 51–57.
- Milgrom, P., Coldwell, S. E., Getz, T., Weinstein, P. & Ramsey, D. S. (1997) Four dimensions of fear of dental injections. *Journal of the American Dental Association* **128**, 756–762.
- Scott, J. & Huskisson, E. C. (1976) Graphic representation of pain. *Pain* **2**, 175–184.
- Svensson, P., Petersen, K. J. & Svensson, H. (1994) Efficacy of topical anesthetic on pain and unpleasantness during scaling of gingival pockets. *Anesth. Prog.* **41**, 35–39.
- Vickers, E. R. & Punnia-Moorthy, A. (1993) Pulpal anesthesia from an application of a eutectic topical anesthetic. *Anesthesiology* **24**, 547–551.
- Zappa, U., Cadosch, J., Simona, C., Graf, H. & Case, D. (1991) In vivo scaling and root planing forces. *Journal of Periodontology* **62**, 335–340.

Address:

Dr David Donaldson
Department of Oral Biological and
Medical Sciences
Faculty of Dentistry
The University of British Columbia
2199 Wesbrook Mall
Vancouver, BC
Canada V6T 1Z3
Fax: + 1 604 822 0736
e-mail: ddonald@interchange.ubc.ca