Evaluation of the diffusion of triamcinolone and demeclocycline through the dentinal tubules and apical foramen: A mass spectrometry study

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Abstract

Aim: The aim of this study was to investigate the diffusion of triamcinolone and demeclocycline from an endodontic paste when used unmodified, versus when combined in equal parts with a calcium hydroxide paste, in terms of diffusion through the dentinal tubules versus through the apical foramen.

Methodology: Medicaments were placed in endodontically prepared roots that were kept in vials of Milli-Q water. The five experimental groups in the study were (1) control – no medicament, (2) medicament containing triamcinolone and demeclocycline (T&D) and occluded apex, (3) T&D paste and patent apex, (4) T&D + calcium hydroxide (Ca(OH)₂) occluded apex, and (5) T&D + Ca(OH)₂ and patent apex. The triamcinolone and demeclocycline concentrations were measured with solid-phase extraction and ultra-high performance liquid chromatography–mass spectrometry, after 1, 3, 8, and 24 h, and after 1 week.

Results: Most of the triamcinolone and demeclocycline diffused through the apical foramen, with sparse diffusion through the dentinal tubules. The T&D paste mixed with Ca(OH)₂ in equal amounts showed greater than the expected 50% reduction in the diffusion of triamcinolone and demeclocycline from mass dilution alone (89% and 80%, respectively).

Conclusions: These results stress the importance of maintaining apical patency, for allowing diffusion of active components of the drugs to target tissues in the periapical environment.

Keywords: Calcium hydroxide; demeclocycline; diffusion; endodontics; ledermix; triamcinolone

INTRODUCTION

The invasion of pathogenic microbes and their by-products into the root canal system leads to local inflammation, which can result in pulpal necrosis.¹ The subsequent inflammation and destruction of the periapical periodontal ligament which follows pulp necrosis is perceived as discomfort or pain.¹ Currently, chemomechanical preparation does not guarantee complete three-dimensional disinfection of the root canal system.² Residual bacteria may be responsible for the persistence of root canal infection and of apical periodontitis.³ A further cause of periapical inflammation is dental trauma.⁴

Interappointment antibiotic-corticosteroid-based pastes such as Ledermix® have been recommended as an adjunct to disinfection and management of postoperative pain.⁵⁻⁷ This antibiotic-corticosteroid paste contains 3.21% (w/w) demeclocycline hydrochloride (demethylchlortetracycline) and 1% (w/w) triamcinolone. It has been widely available since the 1960’s as Ledermix® paste (Lederle Pharmaceuticals,
The triamcinolone component significantly reduces inflammation of the periapical tissues, making Ledermix® paste useful in the management of pain associated with apical periodontitis, and for preventing acute exacerbations of chronic apical periodontits. Triamcinolone reduces osteoclastic activity whereas demeclocycline inhibits collagenase enzymes. This synergistic interaction makes Ledermix® highly effective for inhibiting inflammatory root resorption and periodontal ligament inflammation, and superior to aqueous pastes of calcium hydroxide (Ca(OH)₂).

Demeclocycline is a potent, broad-spectrum, first-generation tetracycline antibiotic, which exerts bacteriostatic effects. It has been reported that the concentration of demeclocycline from Ledermix® achieved in dentin is sufficiently high to give useful antibacterial effects within the 1st day of application. Although demeclocycline has a narrower spectrum of antimicrobial activity than calcium hydroxide, provided that the root canals are instrumented well before the placement of the medicament, both types of medicaments can give worthwhile antibacterial actions.

To relieve the symptoms of inflammation and to inhibit bacterial growth, there must be sufficient diffusion of the steroid and antibiotic components of medicament paste through the radicular dentin and through the apical foramen, to achieve a sufficient concentration at the target periapical tissues. Following chemomechanical preparation of the root canal, residual bacteria and their lipopolysaccharide endotoxins remain in inaccessible areas, such as dentinal tubules, in the cemental canal, and in the apical lesion itself. Furthermore, the presence of triamcinolone is required on the root surface, to reduce the levels of inflammatory mediators and to influence the resorptive cells that are present in the periapical ligament.

Previous work has suggested that the major pathway for movement of triamcinolone and demeclocycline medicament pastes to the external environment of the root was through the dentinal tubules, and that this diffusion was highest in the 1st h. Such rapid diffusion of triamcinolone could be responsible for clinically observed reductions in postoperative pain when used as an intracanal medicament.

A 50:50 mixture of corticosteroid-based antibiotic paste and an aqueous calcium hydroxide paste were advocated by Schroeder in 1981, on the basis that this may leverage the effects of both, or reduce the limitations of the individual medicaments. However, the act of mixing the two pastes gives a mass dilution of both, which may compromise the result. Indeed, while some authors have supported the combination approach, others have raised concerns that a combination could inactivate key active ingredients. Specific mass spectrometry techniques for determining the concentrations of the primary components of dental medicament pastes used in endodontic treatment have been developed and refined. The present study builds on these novel techniques and aims to provide highly accurate diffusion characteristics by measuring the true presence of triamcinolone and demeclocycline from an intracanal medicament paste and to clarify the effect of combining medicaments.

**METHODOLOGY**

**Preparation of teeth**

Fully developed extracted single canal human premolar teeth (n = 41) were collected, with the approval of the institutional ethics committee. No demographic details or identifying information was collected. Teeth were excluded from the study if they had previous restorative/endodontic treatment, or visible defects/cracks. The root surface was debrided gently with an ultrasonic scaler to remove external organic tissue. The roots were then sectioned from the crowns, to give a standardized length of 14 mm.

An ISO size 10 K-file (Dentsply Sirona, United States) was introduced into the root canal until the file was seen at the major constrictor. The working length was determined by subtracting 1 mm from this measurement. The root canals were then prepared using nickel–titanium rotary files (ProTaper® Universal, Dentsply Sirona, United States) to a final size corresponding to a file F2. In between rotary files, an ISO size 15 K-file was used to recapitulate to the working length. The canals were constantly irrigated with 1% sodium hypochlorite (Endosure Hypochlor, Dentalife, Australia) between each file. After the final F2 file, the canals were irrigated with 15% EDTA (EndoPrep, Dentsply Sirona, United States), and the solution was agitated with an EndoActivator® (Dentsply Sirona, United States) for 1 min. A medium tip was used with a 2–3-mm vertical pumping action, as per manufacturer’s instructions. This was then followed by a rinse of 1% sodium hypochlorite at a rate of 2 mL/min for 1 min and a final rinse of distilled water at a rate of 2 mL/min for 3 min.

**Groups**

The roots were then assigned to the five groups using stratified random sampling based on weight, to reduce dentin thickness variations as well as other potential confounding variables [Table 1]:

- Group 1 (control: no medicament with patent apex, n = 5),
- Group 2 (triamcinolone + demeclocycline and occluded apex, n = 9),
- Group 3 (triamcinolone + demeclocycline and patent apex, n = 9),
- Group 4 (triamcinolone + demeclocycline + Ca(OH)₂ and occluded apex, n = 9), and
- Group 5 (triamcinolone + demeclocycline + Ca(OH)₂ and
The roots were then mounted on the lids of 6.5-mL scintillation vials, so that 12 mm of each root extended into the vial when the lid was screwed down fully.

**Experimental protocol using medicaments**

The combination medicament was created by mixing equal volumes of Ledermix® paste and Pulpdent® paste on a glass slide for 30 s, to achieve homogeneity. All medicaments were loaded into a syringe with a 27-gauge needle. The root canals were filled completely. This was verified by observing the material being extruded through the apical foramen. The excess material was immediately and thoroughly removed with an alcohol wipe. To create samples with an occluded apex, sticky wax (Ainsworth, Australia) was applied to occlude the apical foramen completely. As a final step in preparing the roots, an interim material (Cavit G, 3M ESPE, Australia) was used to seal the coronal access.

Fresh Milli-Q water (6 mL) was transferred into scintillation vials using a micropipette. The lid was carefully screwed down, bringing the tooth in full contact with the water. The vials were time stamped and labeled with corresponding root identification tooth number. Vials were incubated in racks at 37°C degrees in conditions of 100% humidity and left undisturbed. At specified time frames of 1, 3, 8, or 24 h, or 1 week, the lid was removed, and the 6-mL water sample kept for analysis. A thin glass probe was used to gently stir the sample water before analysis.

**Sample analysis**

To optimize the detection of demeclocycline and triamcinolone, solid-phase extraction was used alongside ultra-high performance liquid chromatography–mass spectrometry. Hydrophilic lipophilic balance Supelco Supel™ 3 mL cartridge 54182-U SPE tubes (Sigma-Aldrich, United States) were used. The tubes were conditioned by drawing 2 mL of Milli-Q water, followed by 2 mL of a 60:40 methanol: Water mix through each tube. The SPE tubes were then loaded with the remaining 5 mL of sample water, followed by 2 mL of Milli-Q water. The analytes were then eluted from the SPE tubes with 2 mL of acetonitrile into autosampler vials.

Quantification of demeclocycline and triamcinolone was performed in triplicate using an Acquity UPLC system, which consisted of a Quattro Premier XE tandem mass spectrometer with Acquity UPLC system with 2489 TUV (Waters, United States). A calibration curve was generated by running, in triplicate, mixed standards of demeclocycline and triamcinolone at concentrations of 0.5, 1, 2, 5, 10, and 20 ppm (mg/L). This calibration curve was then used to determine the concentration of each component within the samples.

Statistical tests were performed using SPSS (Version 25, IBM Corp., Armonk, N.Y., USA) Statistics software to determine differences between and within groups, using the Kruskal–Wallis H test (Bonferroni corrected Mann–Whitney U test) and Friedman test (Bonferroni corrected Wilcoxon signed-rank), with the significance level set at $P < 0.05$.

**RESULTS**

The greatest diffusion of both triamcinolone and demeclocycline occurred in the group with an patent apex (Group C). This was 58.93 µg of triamcinolone and 4.52 µg of demeclocycline.

Roots with an patent apical foramen (Groups C and E) had greater cumulative diffusion of both triamcinolone and demeclocycline than their occluded apex counterparts (Group B and D) [Table 1]. This indicates that diffusion of these active ingredients in this experimental system occurred largely through the apical foramen.

In terms of the rate of diffusion, in most groups, little or no additional material diffused after the 1st h. As a result, the cumulative diffusion after 1 week (168 h) was mostly due to diffusion that occurred within the 1st h.

When triamcinolone and demeclocycline medicament paste was mixed with Ca(OH)$_2$ paste, the diffusion of both triamcinolone and demeclocycline was affected significantly [Tables 2 and 3]. Rather than the expected 50% reduction, for triamcinolone, there was an approximately ten-fold decrease in the patent apex groups (Groups C vs. E), but only a two-fold decrease (50% reduction) in the occluded apex groups (Groups B vs. D). The same pattern was seen for demeclocycline, with a five-fold decrease in the patent apex group. Of interest, by 1 week, the combination paste group with an occluded apex (Group D) have higher values than the T&D counterpart (Group B), but this difference was not statistically significant.

**DISCUSSION**

This study demonstrates that triamcinolone and demeclocycline diffuse mostly through the apical foramen, rather than through the radicular dentin. Combining
The T&D paste with the Ca (OH)₂ paste gave a reduction in the diffusion, compared to T&D paste alone, over the experimental period of 7 days. In the present study, the roots were kept in an incubator at 37°C with 100% humidity, which was not the case in previous studies. Furthermore, modern chemical analysis methods such as ultra-high performance liquid chromatography–mass spectrometry were used, which should provide a more accurate measurement of small quantities of the analytes of interest.

In roots with a patent apex, there was only a small increase in triamcinolone over time, indicating that only limited diffusion through the dentin of the root was occurring. However, in roots filled with the T&D paste that had an patent apex, 51.57 µg diffused out within the 1st h, and this increased to 58.93 µg by 1 week. This finding suggests that the majority of anti-inflammatory actions from the T&D paste occurs within the 1st h. The concentration of triamcinolone needed to gain a clinically meaningful anti-inflammatory effect on periapical tissues has not been studied in depth, so it is not possible to state with certainty that this dose is always sufficient in the clinical setting. It is, however, useful to know that 51.57 µg of triamcinolone acetonide diffused from the material in a root canal of some 12 mm in length and with final internal dimensions equal to an F2 instrument, when it had a patent apex. A recent animal study concluded that a medicament paste with a minimum concentration of 1% triamcinolone acetonide should give the best treatment outcomes, based on a study of the avulsion and reimplantation of dog teeth. However, the volume of the medicament used in that study is not stated.

In the present study, some diffusion of demeclocycline occurred through the dentinal tubules to the outer root surface, with most of the material diffusing through an patent apical foramen. Despite the initial concentration of demeclocycline (3.21%) being higher than triamcinolone (1%), the rate of diffusion was less for the antibiotic, with only 1.37 µg diffusing through in the 1st h, rising to 4.52 µg by 1 week. These values were less than those reported in previous studies that employed radiolabeled primary components. The study of Abbott reported that 13.67 µg of demeclocycline diffused within the 1st h, and 20.08 µg after 1 week, for roots with a patent apex. It is interesting to note that calcium ions were reported to diffuse through the dentin tubules when assessed using a similar experimental set up.

The slower rate of diffusion of demeclocycline than triamcinolone may be due to the latter binding to dentin, which prevents diffusion occurring. Tetracycline antibiotics form complexes with calcium, and this is exemplified by their incorporation into teeth during odontogenesis. The ability of demeclocycline to bind to root structure has been seen in studies where this component from Ledermix® paste could not readily be

### Table 2: Cumulative mean diffusion of triamcinolone over a 1-week period

| Medicament                        | Triamcinolone diffusion - µg (SD) | Comparison within time periods |
|-----------------------------------|-----------------------------------|------------------------------|
|                                   | 1 h                               | 3 h                          | 8 h                          | 24 h                         | 168 h                        |                                |
| Control (A)                       | 0.00 (0.00)                       | 0.00 (0.00)                  | 0.00 (0.00)                  | 0.00 (0.00)                  | 0.00 (0.00)                  | NS                            |
| T and D paste apex occluded (B)   | 0.50 (1.02)                       | 0.50 (1.02)                  | 0.64 (0.99)                  | 0.64 (0.99)                  | 6.55 (3.07)                  | 168>1.3*                     |
| T and D paste apex patent (C)     | 51.57 (9.50)                      | 51.57 (9.50)                 | 51.57 (9.50)                 | 51.57 (9.50)                 | 58.93 (9.50)                 | NS                            |
| T and D paste + Ca (OH)₂ apex occluded (D) | 0.18 (0.43) | 0.25 (0.60)                  | 0.95 (1.10)                  | 1.33 (1.86)                  | 3.62 (4.42)                  | NS                            |
| T and D paste + Ca (OH)₂ apex patent (E) | 5.53 (4.84) | 5.60 (4.78)                  | 5.60 (4.78)                  | 5.60 (4.78)                  | 6.20 (4.47)                  | NS                            |
| **Comparison between groups**     |                                   |                              |                              |                              |                              |                                |
|                                   | C>A                               | C>A                           | C>A                          | B, C, E>A                     |                                |                                |
|                                   | E>A                               | E>A                           | E>A                          | C>B, D, E”                    |                                |                                |
|                                   | C>B, D, E”                        | C>B, D, E”                    | C>B, D, E”                   | C>B, D, E”                    |                                |                                |
|                                   | E>D”                              | E>D”                          | E>D”                         |                                |                                |                                |

Statistical significance: *P<0.05, **P<0.01, ***P<0.001. NS: Not significant, SD: Standard deviation, Ca (OH)₂: Calcium hydroxide, T and D: Triamcinolone and demeclocycline.

### Table 3: Cumulative mean diffusion of demeclocycline over a 1-week period

| Medicament                        | Demeclocycline diffusion - µg (SD) | Comparison within time periods |
|-----------------------------------|-----------------------------------|------------------------------|
|                                   | 1 h                               | 3 h                          | 8 h                          | 24 h                         | 168 h                        |
| Control (A)                       | 0.00 (0.00)                       | 0.00 (0.00)                  | 0.00 (0.00)                  | 0.00 (0.00)                  | 0.00 (0.00)                  | NS                            |
| T and D paste apex occluded (B)   | 0.04 (0.10)                       | 0.04 (0.10)                  | 0.04 (0.10)                  | 0.04 (0.10)                  | 0.04 (0.10)                  | NS                            |
| T and D paste apex patent (C)     | 1.37 (0.21)                       | 1.37 (0.21)                  | 1.37 (0.21)                  | 1.37 (0.21)                  | 4.52 (1.89)                  | 168>1,3,8,24                  |
| T and D paste + Ca (OH)₂ apex occluded (D) | 0.08 (0.13) | 0.08 (0.13)                  | 0.08 (0.13)                  | 0.08 (0.13)                  | 0.51 (0.61)                  | NS                            |
| T and D paste + Ca (OH)₂ apex patent (E) | 0.54 (0.43) | 0.54 (0.43)                  | 0.54 (0.43)                  | 0.54 (0.43)                  | 0.91 (0.20)                  | NS                            |
| **Comparison between groups**     |                                   |                              |                              |                              |                              |                                |
|                                   | C>A                               | C>A                           | C>A                          | C>A                          |                                |                                |
|                                   | E>B                               | E>B                           | E>B                          | E>B                          |                                |                                |
|                                   | C>B, D, E”                        | C>B, D, E”                    | C>B, D, E”                   | C>B, D, E”                   |                                |                                |
|                                   | E>D”                              | E>D”                          | E>D”                         |                                |                                |                                |

Statistical significance: *P<0.05, **P<0.01, ***P<0.001. NS: Not significant, SD: Standard deviation, Ca (OH)₂: Calcium hydroxide, T and D: Triamcinolone and demeclocycline.
removed using either conventional or sonic activated irrigation.[22] There is also the possibility that the stated concentration on the label may be greater than what is in the paste, due to degradation over time.[28] Currently, there is limited knowledge of the pharmacokinetics of medicaments in the periapical region. Further studies should explore whether an amount of some 4.52 µg of demeclocycline would be sufficient to suppress the growth of endodontic bacteria in the surrounding periapical tissues.

In the present study, roots with a patent apical foramen had significantly higher diffusion than roots with a sealed apex, for both primary components. Penetration of the active ingredients into dentin should have been optimal, since an active irrigation protocol was followed, using Endo activator® to ensure removal of smear layer.[23] Factors such as the extent of smear layer removal, and different size root canals may explain variations in the results of studies of diffusion of steroid and antibiotic components over time. Because of their high molar masses (434.504 g/mol and 464.853 g/mol for triamcinolone acetonide and demeclocycline, respectively), diffusion will be slower than calcium ions or hydroxyl ions.[34] For all situations, an patent apex will enhance release into the periapical tissues.

The combination of a T&D paste with Ca (OH)₂ reduced the rates of release of both triamcinolone and demeclocycline, through both the apical foramen and the dentinal tubules. At 1 week, for roots with an patent apex, the T&D and Ca(OH)₂ combination released only one tenth the dose for triamcinolone and one fifth the dose for demeclocycline, when compared to the T&D paste alone. This finding may be due to multiple factors. As the medicaments are combined in a 50:50 ratio, the concentration of demeclocycline and triamcinolone was effectively halved, resulting in decreased primary component contact with the dentinal tubules, as well as a lower concentration gradient to drive the diffusion. It is also possible that an alkaline pH could affect both the steroid and the antibiotic.[26,27] Binding to calcium ions released from the Ca (OH)₂ paste could have affected release of the tetracycline,[24] and limited its diffusion through the dentinal tubules.[27]

CONCLUSION

The majority of triamcinolone and demeclocycline diffused through the apical foramen, highlighting the importance of a patent apical foramen in allowing this to occur. The rate of diffusion of both triamcinolone and demeclocycline was greatest in the 1st hour after placement. Combining T&D paste and Ca (OH)₂ paste in equal amounts gives a >50% reduction in the two active components, that would be expected from mass dilution alone, with 89% and 80% reductions in the diffusion of triamcinolone and demeclocycline, respectively. Clinicians should avoid combining medicaments as this is detrimental to overall efficacy.

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Conflicts of interest
There are no conflicts of interest.

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