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Allergic reaction to the tetracycline component of Ledermix paste: A case report

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Abstract

Aim Allergy to materials used during root canal treatment is well recognized in the endodontic literature. However, allergy to Ledermix paste, a compound containing triamcinolone (a corticosteroid) and demeclocycline (a tetracycline antibiotic), has not been reported apart from one very recent case in a Letter to the Editor of a journal. The aim of this report is to describe a proven allergic reaction to tetracycline following the use of Ledermix paste as a root canal medicament.

Summary A 33-year old female patient undergoing root canal re-treatment of her right mandibular second premolar tooth experienced symptoms of type 1 allergy following the placement of an intracanal medicament containing a mixture of Ledermix paste and calcium hydroxide [Ca(OH)₂]. Signs of the type 1 allergy included urticaria, pruritus all over the body, general malaise and fever. These all subsided after removing and flushing out the Ledermix paste-Ca(OH)₂ mixture and re-dressing the root canal with Ca(OH)₂ alone.

Allergic scratch tests were performed and these confirmed that the patient was allergic to tetracycline, one of the components of Ledermix paste.

Key learning points

- The tetracycline component of Ledermix may induce a Type-1 hypersensitivity reaction.
- If Ledermix paste is to be used, patients should be asked whether they are allergic to tetracycline.
- Ledermix paste should be avoided in patients known to be allergic to tetracyclines.

Introduction

Several reviews concerning materials and medications used during endodontic treatment that can cause hypersensitivity or allergic reactions have been published in the endodontic literature - among them, are reports of allergy to latex used in rubber dam (Knowles *et al.* 1998, Sunay *et al.* 2006) hypersensitivity to sodium hypochlorite (Kaufman & Keila 1989, Calışkan *et al.* 1994), anaphylactic shock due to formaldehyde and formocresol (Haïkel *et al.* 2000, Ding *et al.* 2013) and the use of AH Plus (Stutz *et al.* 2008), and hypersensitivity to zinc-oxide (Karabucak & Stoopler 2007). As far as the authors are aware following an extensive search of the literature, only one report to date - in the form of a Letter to the Editor (Jetty & Sidebottom 2013) - has been published regarding an allergic reaction to the use of Ledermix paste during root canal treatment.

The use of corticosteroids in endodontics was first suggested by Schroeder (1965). A commercial preparation known as Ledermix paste (Haupt Pharma GmbH, Wolfratshausen, Germany) containing both a corticosteroid and an antibiotic was developed in 1960 (Schroeder & Triadan 1962). It was first released for use in endodontic procedures in Europe and Australia in 1962 (Ehrmann 1965, Bryson *et al.* 2002). There is also a hard-setting form of this material, known as Ledermix cement.

Ledermix paste is a water-soluble paste containing 1% triamcinolone and 3% demeclocycline. Triamcinolone is a highly active steroid providing potent anti-inflammatory action and demeclocycline is a broad-spectrum antibiotic belonging to the tetracycline group, which is effective against a large range of Gram-positive and Gram-negative bacteria (Ehrmann 1965, Bryson *et al.* 2002). The paste has become very popular in many countries as an intracanal medicament for a variety of endodontic procedures because of its ability to diffuse through the dentinal tubules (Ehrmann 1965, Athanassiadis *et al.* 2010a). Studies have demonstrated its ability to reduce acute pain in cases of symptomatic irreversible

pulpitis and for symptomatic apical periodontitis (Negm 2001, Ehrmann *et al.* 2003, Dall *et al.* 2011). The ability of Ledermix paste to reduce inflammatory root resorption after replantation of an avulsed tooth has also been proven (Bryson *et al.* 2002, Day *et al.* 2012). Ledermix cement has been suggested for the treatment of cracked teeth (Thomas 1989, Abbott & Leow 2009) and to reduce dentine hypersensitivity (Thomas 1989, Henry Schein UK Holdings 2013).

Ledermix paste (Haupt Pharma GmbH, Wolfratshausen, Germany) is popular in many countries around the world and it is used either solely or in combination with Ca(OH)_2 for intra-canal dressings in cases of infected root canals, necrosis with incomplete root formation, perforations, root resorption, inflammatory periapical bone resorption and for the treatment of large periapical radiolucent lesions (Schroeder 1981, Abbott 1990). Many dentists mix Ledermix paste with calcium hydroxide [Ca (OH)_2], following Schroeder's (1981) recommendation of this mixture for many endodontic procedures.

Although drugs of the tetracycline group are known for their potential to cause adverse reactions as well as allergies (Steinbruegge & Judson 1980, Jang *et al.* 2010, Miller *et al.* 2011, Lebrun-Vignes *et al.* 2012, Travossos *et al.* 2012), only one recent letter to the Editor of a dental journal has reported an allergy to Ledermix paste due to demeclocycline, one of the Ledermix paste components which belongs to the tetracycline family (Jetty & Sidebottom 2013).

The aim of this case report is to describe a delayed type 1 hypersensitivity reaction that occurred several hours after intracanal dressing with a Ledermix- Ca(OH)_2 mixture, which was later diagnosed as an allergy to tetracycline. In addition, preventive measures to avoid such occurrences are suggested.

Case Report

The patient was treated by a general dentist in Moscow, Russia. The patient was a Caucasian 33-year old woman and a dermatologist by profession. She reported that she was healthy (ASA1) and she was not aware of any allergies. The patient attended a general dentist complaining of slight tenderness in the right mandibular premolar region when chewing. On examination, the dentist noted that the right mandibular second premolar (tooth 45) was slightly tender to percussion. A periapical radiograph (Fig. 1) showed that this tooth had a technically inadequate root canal filling and a periapical radiolucency. The patient thought that the tooth had been root-filled many years previously. The dentist diagnosed the tooth as having a root-filled and infected root canal system with symptomatic apical periodontitis. Root canal re-treatment of this tooth was recommended and the patient consented to this procedure.

Local anaesthetic was not used during any of the root canal procedures for this case. Rubber dam was used throughout each appointment. During the first appointment, the previous root canal filling was removed. The root canal was then irrigated with 10 ml of 3% sodium hypochlorite (Parcan-Septodont Saint-maur-des Fosses, France) followed by 10 mL of saline (Physiologica, Gifrer Barbezat, Moscow, Russia). The canal was dried with paper points (Meta Biomed Inc., Chungbuk, Republic of Korea) and medicated with a mixture of Ca(OH)_2 (Magnesia GmbH, Munich, Germany) and 2% chlorhexidine (Tehnodent, Banja Serbia). The post-operative period was uneventful. Three weeks later, the dentist continued to clean and disinfect the root canal system using K-files (VDW GmbH, Munich, Germany). The root canal was again irrigated with 10 ml of 3% sodium hypochlorite followed by 10 mL of saline irrigation. It was then dried with paper points and re-dressed with the aid of a spiral root filler (VDW GmbH) with a Ca(OH)_2 -Ledermix paste mixture.

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That evening, the patient noticed a rash all over her body. This rash became red and developed into subcutaneous erythematous nodules and pustules. Later that evening, blisters were evident (Fig. 2). The patient sought medical treatment and she was given an injection of an antihistamine (20 mg chloropyramine hydrochloride) which improved the situation by the next morning and during the day. However, that evening, the situation worsened again with exacerbation of the blisters followed by urticaria. The patient received another injection of chloropyramine hydrochloride and she continued to receive further injections twice daily. On the fourth day, the patient returned to her dentist who meticulously irrigated the root canal with saline. The root canal was then re-medicated with Ca(OH)_2 mixed with distilled water. By that evening, the patient felt relief and the pruritus had subsided. The following day, the blisters had dried up and no new signs of erythema appeared.

One month later, the patient was tested for drug allergies by means of scratch tests on the patient's left shoulder to check for reactions to the following drugs: penicillin, sulfamethoxazole, cephalosporin, tetracycline, and fluoroquinolone. A positive reaction was demonstrated only for tetracycline for 12 hours, which was characterized by hyperaemia, oedema and local pruritus with no fever or diarrhoea. The patient was given tablets containing clemastine, a sedative and antihistamine, and the local reaction subsided. Hence, an allergy to tetracycline was confirmed.

Discussion

Ledermix paste has been in use for more than fifty years in many countries. It is very popular as an intracanal medicament for reducing pain (Negm 2001, Ehrmann *et al.* 2003, Dall *et al.* 2011) and bacterial load (Abbott 1990, Athanassiadis *et al.* 2010a, Athanassiadis *et al.* 2010b), to treat external inflammatory root resorption (Bryson *et al.* 2002, Day *et al.* 2012)

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and tooth hypersensitivity (Thomas 1989). In their summary of the product characteristics, the supplier (Henry Schein UK Holdings 2013) warns about potential allergic reactions to Ledermix paste by stating *"Since Ledermix is only administered locally, and the various constituents are leached from the site of application in minute quantities over a long period of time, systemic side effects are extremely rare. However, a few cases of allergic reaction, including anaphylaxis, urticaria, rash and pruritus, have been reported"*. A thorough search of the dental literature found only one report of a case of anaphylactic shock due to allergy to the components of Ledermix paste - this report was in the form of a very recent Letter to the Editor (Jetty & Sidebottom 2013). Excluding this single report, no adverse reactions regarding the use of Ledermix paste have been published elsewhere to date despite this material having been used by dentists for over 50 years. Furthermore, a search in the dental literature for allergic reactions to demeclocycline did not draw any positive results.

Although the intracanal dressing was composed of a mixture of Ledermix paste and Ca(OH)_2 where each could be responsible for the allergic reaction, there are three factors that indicate that only the tetracycline part of the Ledermix paste caused a delayed type 1 hypersensitivity reaction. Firstly, Ca(OH)_2 had already been used in the root canal as the initial medicament in combination with chlorhexidine and the patient had not experienced any signs of allergy during this period. Secondly, after the Ledermix paste- Ca(OH)_2 mixture was removed and the canal was thoroughly irrigated, the root canal was re-dressed with Ca(OH)_2 mixed with distilled water for an entire month. Following this, the allergic reaction subsided and it did not recur – hence, it is unlikely that the hypersensitivity reaction was due to the Ca(OH)_2 . Thirdly, the skin scratch tests unequivocally proved that the patient was allergic to tetracycline.

The 50:50 mixture of Ledermix paste with Ca(OH)_2 was originally suggested by Schroeder (1962) with the aim of broadening the antibacterial activity of Ledermix paste. Calcium

hydroxide is a powder that can be mixed with various vehicles. These vehicles can affect the reaction between the Ledermix paste and the Ca(OH)_2 mixture. In an *in vitro* study, Abbott et al. (1989b) found that mixing a Ca(OH)_2 -methyl cellulose paste with Ledermix paste slowed the release of the active components of Ledermix paste and hence the mixture was more effective as a long-term intracanal dressing than Ledermix paste used alone. In another *in vitro* study, Athanassiadis et al. (2010b) found that a mixture of Ca(OH)_2 -methyl cellulose paste and Ledermix paste maintained its antibacterial activity against *E. faecalis* even in the presence of dentine powder, despite the buffering capacity of dentine. However, Seow (1990) demonstrated reduction in the antibacterial activity against *S. sanguis* and *S. aureus* when Calxyl (a saline-based calcium hydroxide) was mixed with Ledermix paste. These findings raise the question of the effects of different vehicles of Ca(OH)_2 on the Ledermix paste components, and vice versa. Two articles have questioned the validity of mixing Ca(OH)_2 with corticosteroids (Athanassiadis et al. (2011, 2013). In a high-performance liquid chromatography analysis of the interaction of calcium hydroxide in two forms, Pulpdent Paste and calcium hydroxide powder, with Ledermix paste and each of its two components, Athanassiadis et al. (2013) found that the addition of Ca(OH)_2 powder to Ledermix paste affected the antibiotic part of Ledermix paste and caused loss of demeclocycline. The loss ranged from 10% immediately following mixing up to 80% after seven days. When Ledermix paste was mixed with Ca(OH)_2 -methyl cellulose (Pulpdent – Pulpdent Corporation, Watertown, MA, USA), 19% of the demeclocycline was lost after seven days. Adding Pulpdent paste caused a loss of the corticosteroid (triamcinolone acetonide) from 81% immediately after mixing to 96% after 72 hours (Athanassiadis et al. (2011) and the authors raised concerns regarding the effect and understanding of the chemistry of the hybrid paste, the drug interactions, and the breakdown products.

The use of a triple antibiotic paste has been suggested to promote revascularization of the pulp and to treat large peri-radicular radiolucencies (Windley et al. 2005, Taneja & Kumari

2012). One component of the triple antibiotic paste is minocycline which belongs to the tetracycline family. Allergy to minocycline has been reported in the medical literature (Jang *et al.* 2010, Travossos *et al.* 2012). Hence, the use of such antibiotic pastes without verification of the patient's sensitivity to antibiotics might cause serious adverse reactions, especially due to its tetracycline component.

It is possible that some of the medicament or other materials may have extruded through the apical foramen which may have increased the possibility of the allergic reaction occurring. There are several factors that could contribute to such extrusion of material – such as the presence of the previous root filling material or a wide open apical foramen. However, these factors appear unlikely in this case for several reasons. Firstly, it is unlikely that the previous root filling material caused the reaction since it was removed at the first appointment and the allergic reaction did not occur until immediately after the second appointment. In addition, the previous root filling material had only been placed in the coronal half of the canal and it was easily removed. Secondly, although the apical foramen did not appear radiographically to be wide open, it is not possible to determine how wide it was after root canal instrumentation. However, the lack of symptoms after the first appointment in this case suggests that the foramen had not been inadvertently widened. Thirdly, the allergic reaction did not develop until the evening of the second appointment – that is, several hours after the medicament had been placed. If the medicament had extruded through the apical foramen, then it is more likely that the allergic reaction would have occurred immediately or at least very soon after placing the medicament. Fourthly, the delay in onset of the allergic reaction is consistent with the pharmacodynamics of Ledermix paste when placed in the root canal system, and particularly when combined with Ca(OH)_2 . Several studies (Abbott *et al.* 1988, Abbott *et al.* 1989a, Abbott *et al.* 1989b) have shown that the two active components of Ledermix paste take several hours to reach the peri-

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radicular tissues after being placed in the root canal. They diffuse through the dentine and cementum (the major supply route) as well as through the apical foramen (Abbott *et al.* 1988). Release and diffusion is significantly slower when Ledermix is combined with calcium hydroxide and it can last for up to three months (Abbott *et al.* 1989b). The long-term release and diffusion is consistent with the patient's response to the anti-histamine where the symptoms initially subsided somewhat, but they returned the next day. She then had to have repeated injections of the anti-histamine because the allergic reaction persisted until the Ledermix was removed from the canal after which she had rapid relief. Hence, it is unlikely that the apical foramen was wide open or that the Ledermix had extruded through the foramen.

The potential for allergic reactions to drugs and other substances or materials placed in the root canal system highlights the need to take a thorough medical history prior to commencing root canal treatment. This history should include specific questions about allergies in general but particularly allergies to antibiotics, including tetracyclines if these are intended for use during root canal treatment.

Jetty & Sidebottom (2013) in their Letter to the Editor suggested that patients should be informed of the nature of the intracanal medicaments placed in their teeth so that if an allergic reaction occurs, they will be able to provide information to assist the medical team managing the emergency. The case reported above supports this recommendation.

Conclusions

This case report illustrates the importance of taking a thorough medical history before root canal treatment is initiated. This history should include particular questions regarding sensitivity to tetracyclines and any other drugs or materials that may be placed in the root canal system in order to avoid allergic reactions. Patients should also be informed of the

type of intracanal medicaments placed in their root canals in order to assist their emergency management if an allergic reaction does occur.

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Figure Legends

Figure 1 Pre-operative periapical radiograph of the right mandibular second premolar showing a technically inadequate root canal filling and a periapical radiolucency.

Figure 2 The appearance of the patient's leg on the evening that the intracanal medicament was placed. Numerous subcutaneous erythematous nodules are evident.

