

Anaphylaxis due to formaldehyde released from root-canal disinfectant

MAKOTO KUNISADA¹, ATSUKO ADACHI¹, HIROSHI ASANO² AND TATSUYA HORIKAWA³

¹Department of Dermatology, Hyogo Prefectural Kakogawa Hospital, 770-1, Awazu, Kakogawa-cho, Kakogawa, 675-8555, Japan, ²Department of Oral and Maxillofacial Surgery, Kobe University Graduate School of Medicine, 7-5-1, Kusunoki-cho Chuo-ku Kobe, 650-0017, Japan, ³Department of Dermatology, Kobe University Graduate School of Medicine, 7-5-1, Kusunoki-cho Chuo-ku Kobe, 650-0017, Japan

A 50-year-old woman developed anaphylaxis 8 h after application of a paraformaldehyde-containing root canal disinfectant. Radioallergosorbent test showed that she had a high level of formaldehyde-specific IgE in her serum. Prick tests to formaldehyde and paraformaldehyde showed immediate-type responses to both. We reviewed the literature describing cases with anaphylaxis/angioedema caused by formaldehyde in root canal disinfectants and found that about 1/2 of the reported cases developed symptoms over 2 h after dental treatment. We speculated that the delay in the manifestation of her symptoms was possibly due to gradual formaldehyde release from paraformaldehyde and time lag of penetrating and diffusing of formaldehyde outside the dentin. Patch testing showed that she also had delayed-type allergy to formaldehyde, paraformaldehyde and eugenol. Physicians should pay attention to root canal disinfectants, even if anaphylaxis occurs several hours after dental treatment.

Key words: anaphylaxis; delayed-type hypersensitivity; formaldehyde; immediate-type hypersensitivity; paraformaldehyde; root-canal disinfectants; specific IgE; dental patients. © Blackwell Munksgaard, 2002. © Blackwell Munksgaard, 2002.

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Formaldehyde is a well-known allergen, and is a common chemical substance found in a variety of applications (1). It usually causes contact dermatitis mediated by delayed-type allergy (Type-IV) (1). However, there have been rarer reports of immediate-type allergy (Type-I) to formaldehyde (2). We report here a case of anaphylaxis, which proved to be caused by Type-I allergy to formaldehyde in a dental disinfectant. We also reviewed and characterized the clinical features of hypersensitivity to formaldehyde in dental disinfectants.

Case Report

A 50-year-old housewife, who had experienced urticaria following dental treatment several times for the past 3 years, was treated for acute odontitis with a paraformaldehyde-containing root canal disinfectant (Neoparaformpasta[®], Neo Dental Chemical Products Co. Ltd, Tokyo, Japan) and zinc oxide eugenol cement (Neodyne[®], Neo Dental Chemical Products Co. Ltd, Tokyo, Japan) on 21 June 1999. 3 h later, she noticed itchy urticarial erythema on her

limbs and trunk (Fig. 1). On the following day, she was again treated with another paraformaldehyde-containing disinfectant (Periodon[®], Neo Dental Chemical Products Co. Ltd, Tokyo, Japan) and Neodyne[®]. 8 h later, she developed wheal and flare on her entire body accompanied by systemic symptoms, including wheezing, cough, dyspnoea, and dysphagia. Removal of her root canal disinfectant and cement, as well as treatment with intravenous hydrocortisone, cleared her symptoms within 2 days. She was referred to our clinic to find out the causation of her symptoms on 9 December 1999. She had no notable past history except for pollinosis and oral allergy syndrome (OAS) from fruits such as banana and melon. Laboratory tests showed an elevated serum IgE level (580 U/mL, normal <300 U/mL), with normal liver function and blood cell counts. IgE radioallergosorbent tests showed a high titre of specific IgE against formaldehyde (76.6 UA/mL, normal <0.34 UA/mL) and a relatively high titre to Japanese cedar (5.71 UA/mL).

We performed prick tests for various chemicals which were found to be contained in the root canal



Fig. 1. Wheal and flare on both legs appeared with systemic symptoms 8 h after application of a paraformaldehyde-containing root-canal disinfectant.

disinfectants and zinc oxide eugenol cement, including formaldehyde, paraformaldehyde, dibucaine hydrochloride, benzyl alcohol, guaiacol, zinc oxide, calcium hydroxide, rosin, and eugenol (Table 1) on the flexor side of forearm with prick-lancetter (Ewo Care AB, Sweden). Physiological saline and histamine (10 mg/mL, Sigma, Tokyo, Japan) served as controls. A prick test reaction was regarded weakly positive (2+) when it was half of the histamine control, and clearly positive (3+) when the reaction was the same as that resulting from histamine. Prick testing showed positive reaction to paraformaldehyde (1% aq.) and formaldehyde (1% aq.), when assessed at 20 min. Delayed-type responses to formaldehyde, as well as paraformaldehyde, were also noted at the prick test sites 3 days later. To clarify if Type-IV allergy co-existed or not, patch testing was performed with all the chemicals as listed above, and a standard series of fragrances supplied by the Japanese Contact Dermatitis Research Group, using Finn Chambers on Scanpor tape® (Epitest Ltd, Pajjala,

Finland). The application time was 2 days (2D), and the reactions were read at D2, D3 and D7, according to the criteria of International Contact Dermatitis Research Group. Positive reactions were found to formaldehyde (1% aq.), paraformaldehyde (1% aq.), eugenol (1% pet.), eugenol (5% pet.), isoeugenol (5% pet.) and balsam of Peru (25% pet.) (Table 1). Of these agents, paraformaldehyde was contained in Neoparaformpasta® and Periodon®, and eugenol in Neodyne®.

We diagnosed this case as anaphylaxis due to Type-I allergy to formaldehyde containing in dental root-canal fillings. She also had Type-IV allergy to formaldehyde and eugenol, which are contained in root-canal disinfectant and dental cement. We recommended her to avoid formaldehyde and eugenol-containing products, following which she experienced no further allergic symptoms.

Discussion

Formaldehyde is a common chemical substance, which is used extremely widely in a variety of applications. Apart from specific occupational exposures, the most frequent sources of exposures include skin and hair care products, cosmetics, certain cleaning products, medications, permanent press textiles and disinfectants (1). It is also widely used during dental treatment, especially for root canal disinfection (1). It frequently provokes contact dermatitis (1), whereas IgE-mediated response to formaldehyde is rare (2). Kramps *et al.* have described how exposure to formaldehyde, even in high concentration, rarely evokes the production of IgE antibodies (3). This may be one of the reasons why so few cases of Type-I allergy to formaldehyde have been reported in the dermatological field.

The present patient developed urticaria and showed a high level of specific IgE to formaldehyde as well as a positive prick test to formaldehyde, indicating that she had a Type-I allergy to formaldehyde. Most cases of Type-I allergy to formaldehyde have been reported in those who received dental treatment using (para)formaldehyde-containing tooth fillings. The reported cases with anaphylaxis or urticaria caused by formaldehyde in tooth fillings are listed in Table 2 (4–12). 11 of 15 reported cases showed anaphylaxis to formaldehyde, suggesting that Type-I allergy caused by formaldehyde in tooth fillings tends to provoke life-threatening symptoms. Specific IgE to formaldehyde in the patients' sera was significantly elevated in all 6 cases tested and 3 other patients showed positive prick tests. These results suggest that those cases with hypersensitivity to formalde-

Table 1. Skin test results

Chemicals	% vehicle	Prick test	Patch test
Neoparaformpasta [®]			
Paraformaldehyde	1% aq.	2 +	2 +
Dibucaine hydrochloride	1% pet.	—	—
Benzyl alcohol	5% pet.	—	—
Periodon [®]			
Paraformaldehyde	1% aq.	2 +	2 +
Dibucaine hydrochloride	1% pet.	—	—
Guaiacol	5% pet.	—	—
Neodyne [®]			
Zinc oxide	1% pet.	—	—
Calcium hydroxide	1% pet.	—	—
Rosin	20% pet.	—	—
Eugenol	1% pet.	—	2 +
Formaldehyde(JCDRG ^a)	1% aq.	2 +	—
Eugenol (JCDRG)	5% pet.	N.D. ^b	2 +
Isoeugenol (JCDRG)	5% pet.	N.D.	2 +
Balsam of Peru (JCDRG)	25% pet.	N.D.	2 +

^aJCDRG, Japanese Contact Dermatitis Research Group; ^bN.D., not done.

Table 2. Previous reports of Type-I allergy to formaldehyde released from root canal disinfectant

Author	Age/sex	Symptoms	Time lag after tooth treatment (h)	Formaldehyde IgE-RAST	Prick test (scratch)	Patch test
1 AL-Nashi <i>et al.</i> (4)	23/F	Swelling of the face	1	N.D. ^a	N.D.	+ (2% aq.)
2 Forman <i>et al.</i> (5)	57/M	Angioedema	4	N.D.	N.D.	—
3 Ito <i>et al.</i> (6)	66/M	Anaphylaxis	0.7	N.D.	+	+
					(5% aq.)	(5% aq.)
4 Ebner <i>et al.</i> (7)	57/M	Anaphylaxis	1	41.78 ^b	—	—
					(1% aq.)	(1% aq.)
5 Ebner <i>et al.</i> (7)	45/F	Anaphylaxis	10	40.32 ^b	—	—
					(1% aq.)	(1% aq.)
6 Ebner <i>et al.</i> (7)	33/F	Anaphylaxis	5–6	40.54 ^b	—	—
					(1% aq.)	(1% aq.)
7 Fehr <i>et al.</i> (8)	40/F	Anaphylaxis	1.5	+	—	N.D.
8 Fehr <i>et al.</i> (8)	20/F	Urticaria	?	N.D.	—	+
					(10%)	
9 Fehr <i>et al.</i> (8)	39/M	Anaphylaxis	?	N.D.	—	+
					(2%,10%)	
10 Fehr <i>et al.</i> (8)	59/F	Angioedema	?	N.D.	?	—(2%), + (10%)
11 Wantke <i>et al.</i> (9)	67/M	Anaphylaxis	10	Class 2.7	—	—
					(1% aq.)	
12 Sayed <i>et al.</i> (10)	37/F	Urticaria	2–3	N.D.	+	N.D.
					(1% aq.)	
13 Sayama <i>et al.</i> (11)	39/F	Anaphylaxis	2	N.D.	+	+
					(50% aq.)	(50% aq.)
14 Haikel <i>et al.</i> (12)	41/F	Anaphylaxis	Soon after	Class 4 25 KU/L CAP(RIA)	+	—
					(1% aq.)	(1% aq., 1% pet.)
15 Our case	50/F	Anaphylaxis	8	Class 5 76.6 UA/mL	+	+
					(1% aq.)	(1% aq.)

^aN.D., not done; ^bunit unspecified.

hyde are mediated by Type-I allergic response to this chemical.

Another characteristic feature of Type-I allergic response to formaldehyde is that at least 7 patients of 15 reported cases showed allergic symptoms 2–

12 h after dental treatment with paraformaldehyde. It is well known that formaldehyde is gradually released from water soluble paraformaldehyde. Formaldehyde in the root canal can penetrate through the dentin and finally get outside of

the tooth. It has been shown that formaldehyde outside the tooth is detectable 30 min after treatment with paraformaldehyde-containing root canal fillings and logarithmically increased along with time course until 24 h (13). These findings suggest that formaldehyde is gradually released from paraformaldehyde, penetrates through dentin and gradually increases in the circulating blood after root-canal treatment, finally reaching to the threshold to trigger symptoms after 2–12 h, when allergic symptoms are provoked.

7 of 13 cases tested showed a positive patch test to formaldehyde, indicating that they had combined Type-I and Type-IV allergy to formaldehyde, as did the present case. It has been reported that Type-I and Type-IV allergy coexist in individual cases (14,15). In mice, coexistence of Type-I and Type-IV allergy has been generated when a hapten is repeatedly applied on the animal skin (16,17). In this particular animal model, repeated applications of a hapten on the skin are believed to induce a shift of immune response from Th1 to Th2 type. Our patient reported that she had never experienced contact dermatitis from formaldehyde before she developed anaphylaxis. A tendency to develop Type-I allergy to formaldehyde in those with dental canal treatment, as well as haemodialysis (18), suggests that the route of exposure with this agent, whether direct mucous membrane contact or direct infusion into the blood, plays an important role in Type-I sensitization. As our patient had pollinosis and OAS from various fruits, it is possible that she has a predisposition to develop Th2-type immune responses, thereby establishing a Type-I allergy to formaldehyde.

In conclusion, the present case urges us to pay attention to formaldehyde in root-canal disinfectant materials if a patient has Type-I allergy and is under dental care.

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Address:

Atsuko Adachi
Department of Dermatology
Hyogo Prefectural Kakogawa Hospital
770-1, Awazu, Kakogawa-cho
Kakogawa, 675-8555
Japan
Tel: +81 794230001
Fax: +81 794233820
e-mail: faadachi@dd.ij4u.or.jp