



Contents lists available at ScienceDirect

Allergy International

journal homepage: <http://www.elsevier.com/locate/alit>

Letter to the Editor

Anaphylaxis due to thiamine disulfide phosphate, a derivative of vitamin B1; a case report and literature review

Dear Editor,

Vitamin B1 is an essential substance for living organisms, which acts as a coenzyme in the metabolic pathway of glucose and amino acids. Vitamin B1 includes the natural and artificial forms; the former (natural vitamin B1) can be ingested from food, and the latter (vitamin B1 derivative) is artificially synthesized by modifying its structure. Several artificial forms of vitamin B1 are used as a therapeutic preparation in patients' care. Thiamine disulfide phosphate (TDSP) is a vitamin B1 derivative, in which the thiazole nucleus in the natural vitamin B1 (thiamine) is cleaved to maintain a higher blood concentration than natural vitamin B1, and high potential of tissue penetration (Fig. 1a). Although a few cases of type I hypersensitivity to natural vitamin B1 have been reported,^{1–4} no reports on type I hypersensitivity to vitamin B1 derivatives exist in the English-language literature. Here, we report a case of anaphylaxis caused by the intravenous injection of TDSP, in which a histamine release test (HRT) using the patient's basophils was useful for its diagnosis.

An 80-year-old Japanese man was admitted to the emergency department due to the development of anaphylaxis accompanied by generalized pruritus, dyspnea, and decreased blood pressure immediately after given an intravenous injection of Vitamedin®, a vitamin B complex. His serum tryptase level increased significantly to 72.1 µg/L and dropped to 9.8 µg/L at 24 h later. Vitamedin® includes TDSP, 107.13 mg/vial; pyridoxine hydrochloride, 100 mg/vial; cyanocobalamin, 1 mg/vial; D-mannitol, 400 mg/vial. In a skin prick test, wheal formation was found with Vitamedin® at 15 min from the challenge, but none of thiamine hydrochloride; a natural vitamin B1, pyridoxine hydrochloride, cyanocobalamin, and D-mannitol induced significant skin reactions (Supplementary Table 1). The patient developed an anaphylactic shock at 30 min after the prick test.

As an *ex-vivo* examination, HRT was performed using peripheral blood basophils obtained from the patient (Supplementary Methods). The patient's basophils released histamine in response to Vitamedin® in a concentration-dependent manner, while basophils of three healthy volunteers did not (Fig. 1b). No histamine release from basophils of the patient was observed in response to thiamine hydrochloride (natural vitamin B1 [nVit. B1]), pyridoxine hydrochloride (Vit. B6), cyanocobalamin (Vit. B12), and D-mannitol. Next, we performed HRT using vitamin B1 derivatives, including TDSP, thiamine disulfide, benfotiamine, and cocarboxylase. TDSP induced histamine release from the patient's basophils

in a similar concentration-dependent manner to Vitamedin® did (Fig. 1c). Thiamine disulfide, benfotiamine, and cocarboxylase induced marginal, and dose-independent release of histamine. Based on these results, we diagnosed this case as anaphylaxis due to type I hypersensitivity to TDSP, a derivative of vitamin B1 contained in Vitamedin®.

Type I hypersensitivity to vitamin B1 has been reported in cases reactive to the natural form of vitamin B1.^{1–4} Fernandez *et al.* presented a case of anaphylaxis to the natural vitamin B1.⁴ They demonstrated histamine release from the patient's basophils, and the presence of IgE antibody in sera of the patients to natural vitamin B1. In addition, two cases of type I hypersensitivity to vitamin B1 derivatives have been reported in Japanese^{5,6} (Table 1), but no report was found in literature accessible via PubMed in English. All of these two patients and our case developed anaphylactic shock, and showed hypersensitivity to TDSP by skin tests, such as intradermal test, prick test, and/or patch test (Table 1). We further confirmed the hypersensitivity to TDSP by HRT using basophils of the patient. Skin tests may detect non-specific response to a culprit, and the detection of specific serum IgE binding may not necessarily be associated with the histamine-releasing activity. Thus, HRT may be a useful option to detect hyperreactivity to TDSP that can be safely performed *ex-vivo*, especially in cases with a risk of anaphylaxis by skin tests, like ours. These results of the skin test and HRT strongly imply that the pathomechanism of the immediate reaction to TDSP is related to mast cell activation mediated by specific IgE antibody.

Regarding antigenicity with respect to vitamin B1, our case showed no cross-reactivity of TDSP to the natural vitamin B1 and the other vitamin B1 derivatives both in the prick test and HRT. This fact argues against it being hypersensitivity to the basic structure of vitamin B1 such as pyrimidine nuclei and cleaved thiazole nuclei. In addition, the lack of reactivity to thiamine disulfide and benfotiamine ruled out the antigenicity of structures of disulfide groups and phosphate groups in TDSP. Previous reports have also shown no cross-reactivity between TDSP and other vitamin B1 formulations (Table 1). Therefore, the antigenicity of TDSP may be attributed to a structure unique to TDSP, or the binding ability with proteins to form a hapten. A sensitization route for TDSP is another matter of discussion. Takahashi *et al.* presented a case of anaphylaxis to TDSP with one-year history of repeated intravenous administration of vitamin B complex containing thiamine disulfide, Normicamin®.⁵ Another case reported by Hiratani *et al.* developed allergic reactions after the second administration of Vitamedin®.⁶ Although a history of vitamin B1 formulation use was unknown in our case, the previous cases suggested sensitizations by past intravenous administration of vitamin B1 derivatives (Table 1).

Peer review under responsibility of Japanese Society of Allergy.

<https://doi.org/10.1016/j.alit.2022.01.004>1323–8930/Copyright © 2022, Japanese Society of Allergy. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

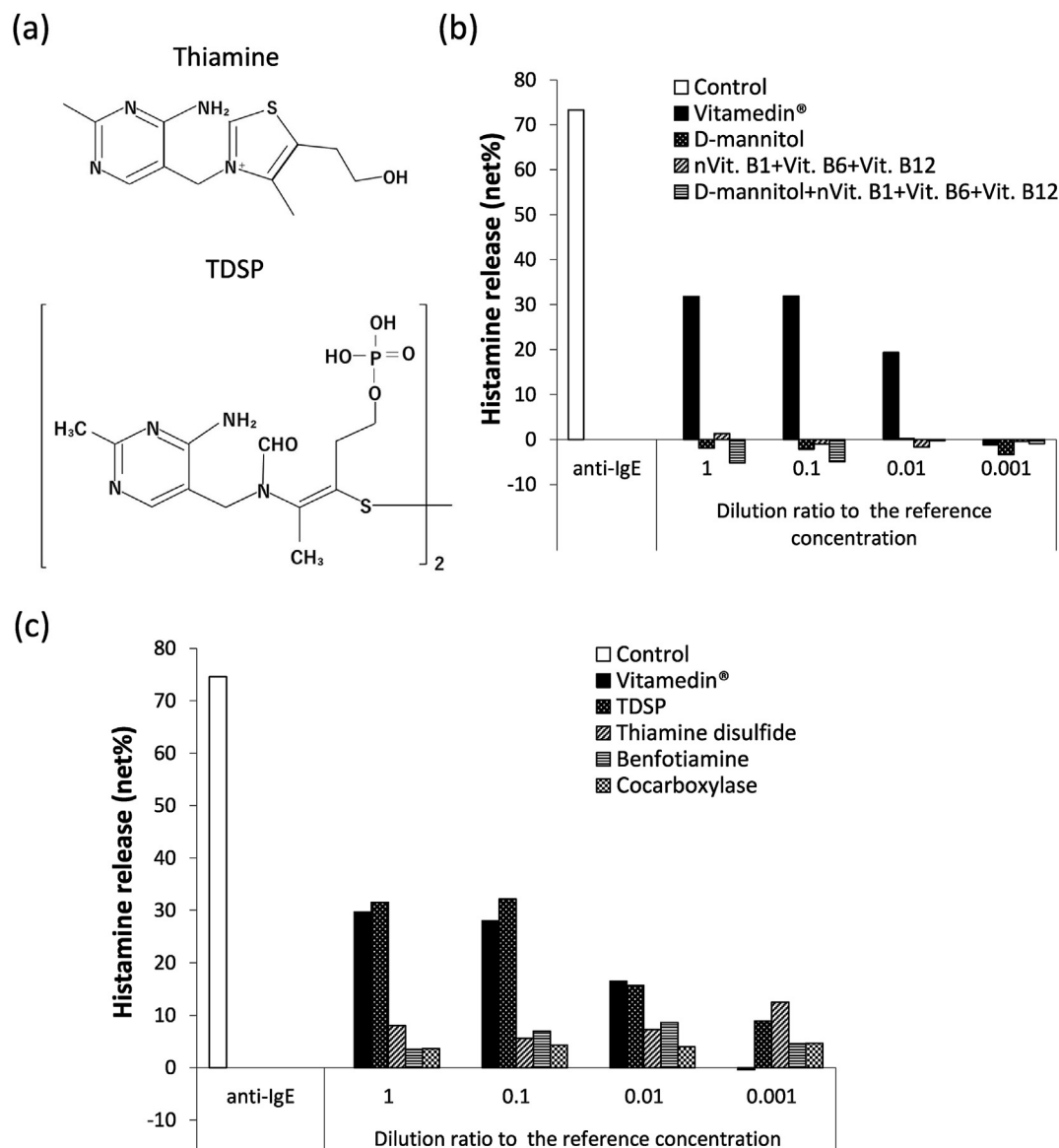


Fig. 1. (a) Structures of natural vitamin B1, thiamine, and a vitamin B1 derivative, thiamine disulfide phosphate (TDSP). (b) The histamine release test (HRT) data of the patient for Vitamedin®. The reference concentration of each reagent was as follows; Vitamedin® 1 vial/2 L, D-mannitol 200 µg/ml, thiamine hydrochloride (nVit. B1) 50 µg/ml, pyridoxine hydrochloride (Vit. B6) 50 µg/ml, cyanocobalamin (Vit. B12) 0.5 µg/ml. (c) The HRT data of the patient for Vitamin B1 derivative. The reference concentration of each reagent was as follows; Vitamedin® 1 vial/2L, thiamine disulfide phosphate 5 mg/ml, thiamine disulfide 5 mg/ml, benfotiamine 5 mg/ml, and cocarboxylase 5 mg/ml. Vitamedin® 1 vial contains thiamine disulfide phosphate, 107.13 mg; pyridoxine hydrochloride, 100 mg; cyanocobalamin, 1 mg; D-mannitol, 400 mg.

Table 1
Review of the literature on immediate reaction to thiamine disulfide phosphate (TDSP).

Reference	Age	Sex	Clinical symptoms	Skin tests	Ex-vivo test	Causative agent, route of administration	Cross reactivity to other vitamin B ₁ formulation		History of vitamin B ₁ formulation use
							Natural vitamin B ₁	Vitamin B ₁ derivatives	
Our Patient	80	M	Anaphylaxis	Prick test, positive	HRT, positive	TDSP, i.v.	None	None	Unknown details, oral
Takahashi <i>et al.</i> ⁵	56	M	Anaphylaxis	Intradermal test, positive Patch test, positive	Not done	TDSP, i.v.	None	None	Nornicicamin®, i.v.
Hiratani <i>et al.</i> ⁶	54	F	Anaphylaxis	Intradermal test, positive Patch test, negative	Not done	TDSP, i.v.	None	None	Vitamedine®, i.v.

M, male; F, female; HRT, histamine release test; i.v., intravenous injection; oral, oral administration.

Although vitamin B1 derivatives are generally safe, TDSP may cause a severe reaction of type I hypersensitivity. Skin tests are relatively safe and easy-to-perform *in-vivo* examinations to detect type I hypersensitivity to TDSP; however, HRT, an *ex-vivo* assay, is safer and could be an option in highly sensitive cases, especially with a prior history of anaphylaxis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2022.01.004>.

Conflict of interest

AA received materials for this study from Daiichi Sankyo, and Alfresa Pharma Corporation. The rest of the authors have no conflict of interest.

Asuka Amano ^{a,b}, Shunsuke Takahagi ^{c,*}, Hitomi Kinoshita ^b,
Rie Nakamura ^b, Kaori Ishii ^c, Michihiro Hide ^{c,d}

^a Department of Dermatology, JA Hiroshima General Hospital, Hiroshima, Japan

^b Department of Dermatology, National Hospital Organization Kure Medical Center and Chugoku Cancer Center, Hiroshima, Japan

^c Department of Dermatology, Institute of Biomedical & Health Sciences, Hiroshima University, Hiroshima, Japan

^d Department of Dermatology, Hiroshima Citizens Hospital, Hiroshima, Japan

* Corresponding author. Department of Dermatology, Institute of Biomedical & Health Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan.

E-mail address: shunstkt@hiroshima-u.ac.jp (S. Takahagi).

References

- Rodriguez-Fernandez A, Sanchez-Dominguez M, Noguera-Mellado B, Rojas-Perez-Ezquerro P. Urticaria by thiamine (vitamin B1). *Allergol Int* 2018;**67**: 276–7.
- Aurich S, Simon JC, Treudler R. A case of anaphylaxis to intramuscular but not to oral application of thiamine (vitamin B1). *Iran J Allergy Asthma Immunol* 2018;**17**: 94–6.
- Juel J, Pareek M, Langfrits CS, Jensen SE. Anaphylactic shock and cardiac arrest caused by thiamine infusion. *BMJ Case Rep* 2013;**2013**:bcr2013009648.
- Fernandez M, Barceló M, Muñoz C, Torrecillas M, Blanca M. Anaphylaxis to thiamine (vitamin B1). *Allergy* 1997;**52**:958–60.
- Takahashi Y, Kambara T, Fujimura N, Nakamura K, Hirokado M, Matsukura S, et al. [A case of anaphylactic shock due to thiamine monophosphate disulfide, a derivative of vitamin B1]. *J J Environ Dermatol Cutan Allergol* 2012;**64**: 368–72 (in Japanese).
- Hirata M, Hiraga T, Terasawa H, Hosokawa O, Mitsuto O. [A case of anaphylactic shock due to vitamin B1 derivative (thiamine monophosphate disulfide)]. *Arerugi no rinsho [Arerugi no rinsho The Allergy in Practice]* 1992;**12**:1036–9 (in Japanese).

Received 4 January 2022

Received in revised form 24 January 2022

Accepted 28 January 2022

Available online xxx

Supplementary data

Supplementary Methods

Reagents

Vitamedin[®] and thiamine disulfide phosphate (TDSP) were provided by Daiichi Sankyo company, Tokyo, Japan. D-mannitol, thiamine hydrochloride, pyridoxine hydrochloride, cyanocobalamin, and cocarboxylase were purchased from FUJIFILM Wako Pure Chemical Corporation, Osaka, Japan. Thiamine disulfide, and benfotiamine were purchased from Combi-Blocks, CA, USA.

Histamine release test (HRT)

HRT was performed by using basophils obtained from our patient and healthy volunteers, as described previously¹. Briefly, peripheral blood leucocytes containing about 1% basophils were collected by specific gravity using 1% methyl cellulose solution. Cells were suspended in the reaction buffer; 136mM sodium-chloride / 10mM HEPES / 0.1% glucose / 0.03% human serum albumin / 2mM CaCl₂ / 1mM MgCl₂. The suspended cells were stimulated at 37 °C for 40 minutes with 0.33 µg/ml of goat anti-human IgE antibody (Bethyl Laboratories, TX, USA), or the diluted concentration series of each antigen such as vitamedin[®], D-mannitol, thiamine hydrochloride, pyridoxine hydrochloride, cyanocobalamin, TDSP, thiamine disulfide, benfotiamine, or cocarboxylase. These antigens were pre-incubated with self-serum at 10% concentration at 37 °C for 30 minutes. After incubation, the cells and the supernatant were obtained by centrifugation. Each separated sample was mixed with HClO₄ to a final concentration of 2.5% to denature excess proteins. Following incubation for 30 min at room temperature, histamine was extracted in the supernatant by centrifugation, and analyzed for its amount by using high performance liquid chromatography (HPLC). The HPLC system consisted of an LC-20A (Shimadzu, Kyoto, Japan) with VP-ODS column (Shimadzu) and RF-10Axl fluorescence detector (Shimadzu), operating at an emission wavelength of 440 nm and an excitation wavelength of 360 nm. The percentage of histamine release was calculated with the ratio of the amount of histamine in the supernatant to the total amount of histamine in the supernatant and cells.

1. Hide M, Tanaka T, Yamamura Y, Koro O, Yamamoto S. IgE-mediated hypersensitivity against human sweat antigen in patients with atopic dermatitis. *Acta Derm Venereol* 2002; **82**: 335-40.

Supplementary Table 1. Skin reactions in prick test. Vitamedin[®] contains thiamine disulfide phosphate (TDSP), 107.13 mg; pyridoxine hydrochloride, 100 mg; cyanocobalamin, 1 mg; D-mannitol, 400 mg, in a vial.

Test sample	Mean wheal diameter (mm)	
	Our patient	A healthy volunteer
Vitamedin [®] (1 vial/20 ml)	22	0
Thiamine hydrochloride (5 mg/ml)	0	0
Pyridoxine hydrochloride (5 mg/ml)	0	1.5
Cyanocobalamin (50 µg/ml)	0	0
D-mannitol (20 mg/ml)	0	0
Histamine (10 mg/ml)	6.5	6
Saline	0	0