

# Acute Allergic Reaction due to Milk Proteins Contaminating Lactose Added to Corticosteroid for Injection

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## ABSTRACT

We encountered two patients with severe cow's milk allergy who reacted strongly to an injection of methylprednisolone sodium succinate (Sol-Medrol 40 mg<sup>®</sup> Pfizer, Japan). They came to our hospital because of an asthmatic attack or urticaria and were treated with Sol-Medrol 40 mg<sup>®</sup>. After the injection, the allergic reaction was immediate. Skin prick tests demonstrated that the  $\beta$ -lactoglobulin contaminating the lactose of the drug preparation caused the immediate allergic reaction.

## KEY WORDS

allergic reaction, cow's milk allergy, lactose, methylprednisolone sodium succinate,  $\beta$ -lactoglobulin

## INTRODUCTION

Patients who have food allergies need to pay particular attention to their intake not only of foods but also of pharmaceutical drugs. Usually, it is comparatively safe for children with milk allergies to ingest drugs containing lactose, but not if the lactose is contaminated with milk protein.

Methylprednisolone sodium succinate (Sol-Medrol<sup>®</sup>) is frequently used for allergic patients in Japan. When a methylprednisolone sodium succinate injection is administered to children with exacerbation of bronchial asthma or with an allergic predisposition, 40 mg of the drug is usually used, since this is the minimum dose. Pharmacists produce 4 different doses of methylprednisolone sodium succinate, and lactose is found only in the 40 mg preparation (25 mg of lactose per vial).

In this report, we describe two cases of severe milk allergy in which an immediate allergic reaction due to the lactose in Sol-Medrol 40 mg<sup>®</sup> was diagnosed.

## CLINICAL SUMMARY

### CASE 1

An 8-year-old girl was referred to the Emergency De-

partment at Fujisawa City Hospital in September 2006 because of a high fever, cough and wheezing.

In early childhood, she was diagnosed as having bronchial asthma, atopic dermatitis and a food allergy, and was instructed to avoid consuming milk, buckwheat, beef, and processed foods containing these. It is uncertain whether the patient had episodes of anaphylaxis due to food allergy.

Acute bronchitis and a moderate asthmatic attack were diagnosed.  $\beta_2$ -agonist inhalation was not effective, and therefore a 30 mg injection of Sol-Medrol 40 mg<sup>®</sup> was administered. This was followed by the rapid spread of urticaria all over her body.

We attributed this to an allergic reaction to the medicine. When the patient was given hydroxyzine hydrochloride intravenously and a hypodermic injection of epinephrine, her condition improved immediately.

### CASE 2

A 3-year-old boy was referred to the Emergency Department of Fujisawa City Hospital in September 2006 because of urticaria in the neck. He had allergies to various plants and had had episodes of anaphylaxis at 2 years of age due to exposure to some plants. He

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**Table 1** Results of skin prick test in Case 1

	SPT*	Serum Specific IgE
Milk	++	> 100 UA/ml
Egg white	++	13.4 UA/ml
Egg yolk	++	ND
Soybean	—	2.93 UA/ml
Wheat	—	3.57 UA/ml
Buckwheat	+	3.53 UA/ml
Beef	ND**	0.34 UA/ml
Dermatophagoides pteronyssinus	ND	> 100 UA/ml
House dust	ND	> 100 UA/ml
Alternaria	ND	17.3 UA/ml
Japanese cedar pollen	++	ND
Sol-Medrol 40 mg <sup>®</sup>	+	ND
Sol-Medrol 125 mg <sup>®</sup>	—	ND
Decadron <sup>®</sup>	—	ND
Solu-Cortef <sup>®</sup>	—	ND
Predonine <sup>®</sup>	—	ND

SPT\* : Skin prick test, ND\*\* : NOT DONE.

also had food allergies and avoided consuming milk, egg, soybean, sesame, peanut, shrimp, and crab. He had no history of anaphylaxis due to food allergy and had no symptoms when he ate cornflakes containing lactose when he was 3 years of age.

The urticaria appeared when he took a walk around a park which had a variety of plants. He had no complaints of cough, nasal discharge, or eye symptoms. He came to the hospital after having taken hydroxyzine hydrochloride. There was urticaria on his neck, although he had no respiratory distress, and his general condition was not poor. He was diagnosed with an acute allergic reaction to some plants, and 20 mg of Sol-Medrol 40 mg<sup>®</sup> was injected. After that, rash and urticaria spread rapidly all over his body.

We suspected that the rash was caused by the injection of Sol-Medrol 40 mg<sup>®</sup>, and therefore we administered hydroxyzine hydrochloride intravenously. The rash improved immediately.

### LABORATORY FINDINGS

The laboratory data in Case 1 showed an abnormal increase in leukocytes and C reactive protein because of acute bronchitis (white blood cell count 15,800/mm<sup>3</sup>, C-reactive protein 0.9 mg/dl). Serum total IgE antibody was 1610 UA/mL and serum-specific cow's milk-IgE was over 100 UA/mL. (Serum-specific IgE antibody was measured with the Phadia CAP RAST system, Phadia diagnostics; the lower limit of detection was 0.35 UA/mL and the upper limit of detection was 100 UA/mL).

The laboratory data in Case 2 were normal except that serum-specific milk-IgE was over 100 UA/mL.

Serum total IgE was 13000 UA/mL in 2005.

We hypothesized that Sol-Medrol 40 mg<sup>®</sup> was the cause of the allergic reactions and performed skin prick tests on both of these patients after their symptoms stabilized.

### METHODS

On the basis of the patients' histories, we used antigenic liquid (Torii, Japan) and administered the following five steroids for injection: methylprednisolone sodium succinate (Sol-Medrol 40 mg<sup>®</sup>), methylprednisolone sodium succinate (Sol-Medrol 125 mg<sup>®</sup>), hydrocortisone sodium succinate (Solu-Cortef 100 mg<sup>®</sup>), dexamethasone (Decadron 2 mg<sup>®</sup>), and prednisolone sodium succinate (Predonine 10 mg<sup>®</sup>). Only methylprednisolone sodium succinate (Sol-Medrol 40 mg<sup>®</sup>) contained lactose.

For Case 2, we also tested for lactose produced as described in the Japanese Pharmacopoeia.

The needles used for the prick tests were standard, regularly used, bifurcated needles made by ALO Laboratories, Inc (OH, USA). Results were considered strongly positive if the resulting wheal measured 10 mm or more in diameter, and positive if it was 5 mm or more in diameter, or was at least twice the size of the reaction to the control.

We also examined whether the milk protein was contained in Sol-Medrol 40 mg<sup>®</sup> and 1 g of lactose produced according to the Japanese Pharmacopoeia. We performed a quantitative analysis of  $\beta$ -lactoglobulin with the Morinaga specific material measurement kit at Doshisha Women's College of Liberal Arts.

### RESULTS

In Case 1, strongly positive results were obtained for milk, while a positive result was obtained for Sol-Medrol 40 mg<sup>®</sup>, and a negative one for Sol-Medrol 125 mg (Table 1).

In Case 2, the results were strongly positive for milk and lactose, positive for Sol-Medrol 40 mg<sup>®</sup>, and negative for Sol-Medrol 125 mg<sup>®</sup>. The reason why the test for Predonine was positive is unknown (Table 2).

The results of a quantitative analysis of  $\beta$ -lactoglobulin are shown in Table 3.  $\beta$ -lactoglobulin was detected in Sol-Medrol 40 mg<sup>®</sup> (112.5 ng of  $\beta$ -lactoglobulin per vial), and lactose (1.35  $\mu$ g of  $\beta$ -lactoglobulin per gram of lactose).

### DISCUSSION

From the results of skin prick tests and the quantitative analysis of  $\beta$ -lactoglobulin, we concluded that the lactose in Sol-Medrol 40 mg<sup>®</sup> was contaminated by milk protein and caused immediate allergic reactions in the two cases. Especially in Case 1, it is possible that acute bronchitis played a part in the allergic reaction. In 2002, Morishita *et al.* reported that anaphy-

**Table 2** Result of skin prick test in Case 2

	SPT	Serum Specific IgE
Milk	++	> 100 UA/ml
Egg white	++	> 100 UA/ml
Egg yolk	++	31.1 UA/ml
Ovomucoid	++	19 UA/ml
Wheat	++	27.3 UA/ml
Soybean	++	ND
Shrimp	++	ND
Buckwheat	++	ND
Cypress	ND	11.3 UA/ml
Orchard grass	ND	27.4 UA/ml
Ragweed	ND	44.5 UA/ml
Mugwort	ND	17.3 UA/ml
Golden rod	ND	29 UA/ml
Lactose	++	ND
Sol-Medrol 40 mg <sup>®</sup>	+	ND
Sol-Medrol 125 mg <sup>®</sup>	-	ND
Decadron <sup>®</sup>	-	ND
Solu-Cortef <sup>®</sup>	-	ND
Predonine <sup>®</sup>	+	ND

laxis due to lactose in Sol-Medrol 40 mg<sup>®</sup> was diagnosed in a 4-year-old Japanese boy who had cow's milk allergy.<sup>1</sup> The authors performed skin prick tests on the patient and obtained a positive result for Sol-Medrol 40 mg<sup>®</sup> and a negative result for Sol-Medrol 125 mg<sup>®</sup>. These results matched those in our two cases.

We ascertained that the lactose produced as described in the Japanese Pharmacopoeia contains milk protein as a result of imperfect purification. According to the manual of the Japanese Pharmacopoeia concerning lactose,<sup>2</sup> the protein mixture is expected to be eliminated during the manufacturing process, and there is no possibility for milk protein to be present in the lactose. Therefore, the product information inserts do not caution patients with milk allergy about the possibility of an allergic reaction to milk proteins.

Fiocchi *et al.* performed skin prick tests for lactose in 24 patients with cow's milk allergy, and found that the prick tests were negative in all the patients, although 13 of them had a medical history of anaphylaxis and the mean of their serum cow's milk specific-IgE concentrations was 25.7 UA/ml.<sup>3</sup> He concluded that even children with cow's milk allergy were clinically tolerant of lactose and could safely consume foods and drugs containing it. However, we would suggest that the results of their skin prick tests may have been affected by lower specific IgE levels than was observed in our two patients.

**Table 3** Quantitative analysis of  $\beta$ -lactoglobulin

	$\beta$ -lactoglobulin
Sol-Medrol 40 mg	112.5 ng/vial
Lactose	1.35 $\mu$ g/g

If the lactose for ingestion contains  $\beta$ -lactoglobulin, it is usually safe for children with milk allergy because the lactose passes through the immune portion of the digestive system. However, when a small amount of  $\beta$ -lactoglobulin is injected directly, it is bound to cause an allergic reaction in sensitive patients. Moreover, the lactose in Sol-Medrol 40 mg<sup>®</sup> is at a higher concentration than that determined by a quantitative analysis of  $\beta$ -lactoglobulin according to the Japanese Pharmacopoeia, as shown in Table 3. This is a very important fact for both the patient and physician.

Lactose is commonly used as an inactive ingredient in many pharmaceutical formulations including tablets, suspensions, dry powder inhalers, and medicines for injection. A previous report described a cow's milk allergy in an asthmatic patient who had an anaphylactic reaction to the milk protein in a dry powder inhaler containing both salmeterol and fluticasone.<sup>4</sup>

In conclusion, when a patient with severe cow's milk allergy is treated with a drug, especially when that drug is intravenously injected, only a preparation entirely free of lactose should be used. Although drug additives such as lactose are necessary for stabilization or activation of the constituents of preparations, the fact that some additives cause severe allergic reactions must be constantly borne in mind.

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