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Cow's milk allergy as a cause of anaphylaxis to systemic corticosteroids

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Immediate IgE-mediated allergic reactions to corticosteroids are rather uncommon, whereas causative agents usually involve the native steroid molecule or a pharmaceutical excipient, in most cases a succinate ester bound to methyl-prednisolone or hydrocortisone (1, 2). We here report two cases of immediate reaction

Lactose-free corticosteroid preparations should be exclusively used when treating patients with severe cow's milk allergy.

to methyl-prednisolone, attributed to milk allergen contamination.

A 9-year-old boy with a history of severe persistent cow's milk allergy (CMA) was seen at the Emergency Department due to a virus-induced asthma exacerbation presented with fever, wheezing & moderate dyspnea. The boy was administered nebulized salbutamol, as well as 40 mg of methyl-prednisolone by intravenous injection. Paradoxically, wheezing deteriorated, along with a slight fall in arterial blood oxygen saturation, so the boy was given another course of the same medication on assumption of clinical under-responsiveness. Within a few minutes the patient acutely collapsed, with hypotension, cyanosis and respiratory arrest and had to be immediately transferred to the IC Unit, where he was given epinephrine intramuscularly and was eventually intubated.

Another patient, a 7-year-old boy with severe CMA was similarly treated with salbutamol and intravenous administration of 40 mg methyl-prednisolone, following clinical diagnosis of a virus-induced asthma exacerbation. The therapeutic intervention resulted in a full-blown anaphylactic reaction, with aggravation of dyspnea & wheezing,

immediate urticarial rash, emesis and ultimately hypotension.

Both children were evaluated within the next 6 months for assumed IgE-mediated reactivity to methyl-prednisolone. Skin testing (skin prick and intradermal tests when indicated) was performed using seven different corticosteroids to evaluate cross-reactivity pattern and identify the culprit agent (Table 1). Sensitization to the native steroid molecule and to the succinate ester was ruled out by negative skin tests, while both patients exhibited positive skin response exclusively to lactose-containing preparations.

Subsequent drug provocation tests were negative in both patients for a full therapeutic dose (125 mg) of non-lactose containing, otherwise identical to the one that elicited the reaction, succinylated methyl-prednisolone preparation (Solu-Medrol 125 mg, Pfizer). Diagnostic drug challenges with the lactose-containing preparation (Solu-Medrol 40 mg, Pfizer) were considered unethical due to the recent history of severe systemic reaction and were not performed.

By employing a highly sensitive ELISA assay (Veratox Total Milk Elisa kit; Neogen, St. Joseph, MI, USA, limit of detection = 0.5 ppm), we detected

Table 1 Skin testing results in both patients with acute reaction to lactose-containing succinylated methyl-prednisolone

Drug tested	Original concentration	SPT		ID		Lactose-containing
		1/10	1/1	1/100	1/10	
Methyl-prednisolone sodium succinate 40 mg	40 mg/ml	–	+			Yes
Methyl-prednisolone sodium succinate 125 mg	62.5 mg/ml	–	–	–	–	No
Methyl-prednisolone acetate 80 mg	40 mg/ml	–	–	–	–	No
Hydrocortisone sodium succinate 250 mg	125 mg/ml	–	–	–	–	No
Dexamethasone sodium phosphate 8 mg	4 mg/ml	–	–			No
Prednisolone 25 mg	25 mg/ml	–	–			No
Methyl-prednisolone tablet 4 mg		+	+			Yes
Cow's milk extract			+			Yes

traces of milk proteins, within the range of 2.0–3.5 ppm, in samples from all five batches tested of the implicated product (Solu-Medrol 40 mg, Pfizer), confirming our hypothesis of milk allergen contamination.

Although uncommonly, pharmaceutical lactose, contained as an excipient in corticosteroid preparations may be an iatrogenic cause of anaphylaxis in children with severe CMA, due to milk protein contamination (3, 4). This is particularly relevant, since patients with severe CMA exhibit increased risk of concurrent asthma or other food allergies (5, 6). In the case of an acute allergic event or an asthma exacerbation, these patients are reasonable candidates for systemic administration of (possibly lactose-containing) methylprednisolone. Given that the concurrent asthma exacerbation may potentially decrease threshold for anaphylaxis, intravenous injection of even minute amounts of cow's milk protein may be sufficient to elicit a severe reaction, e.g. by further aggravating preexisting bronchospasm. In any case, increased

caution is warranted, as there is marked risk of mistaking the allergic reaction for apparent under-responsiveness to medication. This may justify additional administration of the allergen-containing drug, as in the case of one of our patients, especially since product information inserts typically do not caution patients with milk allergy about the rare possibility of an allergic reaction to contained milk proteins. It is of paramount importance that non-lactose containing preparations (Table 1) are exclusively used when treating such patients.

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