

ICS and β_2 agonists may augment bronchodilation,⁴ which may further support its use in the management of asthma.

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Excipient allergy and importance of complete allergy histories



We read with great interest Sompornrattanaphan et al's¹ report on a case of fatal anaphylaxis from an amoxicillin-clavulanic acid (AMX-CL) drug provocation test (DPT) after a prior negative DPT. The authors postulate that the positive DPT with AMX-CL 300-21.45 mg was compatible with CL resensitization, as the patient previously tolerated a prior DPT with AMX-CL 1520-216.6 mg without reaction. We agree that the initial DPT dose was enough to confirm a negative result but question the seemingly rare possibility of resensitization.

Conversely, we caution the potential diagnosis of excipient allergy and wish to highlight the importance of reporting a complete drug allergy history. We had previously reported the importance of excipient testing in steroid allergy, but we believe that it needs to be considered in other drug allergies also.^{2,3}

In their report, the authors did not disclose the exact formulation of AMX-CL used in the DPTs. However, the different

ratios of AMX:CL suggest that the formulations in both DPTs were different. For example, if hypothetically, 19 mL of AUGMENTIN SUSPENSION (AMX:CL 400:57 mg/5 mL; GlaxoSmithKline, London, UK) was used for the initial negative DPT, whereas 2.5 mL of AUGMENTIN ES (AMX:CL 600:42.9 mg/5 mL; GlaxoSmithKline) was used for the positive DPT, then excipients only present in the latter formulation may have been the causative allergen instead (Table I). In this hypothesized scenario, carboxymethylcellulose (CMC) may have been the true allergen and CMC-containing eye drops for skin testing may have been useful.²

Excipient allergies can be easily missed or overlooked if the excipient list of each formulation is not examined. This is especially a concern in countries where excipient lists are not mandated by law or local regulatory bodies. We also encountered a case of anaphylaxis after administration of AMX-CL and suspected an excipient allergy. A 38-year-old woman suffered from life-threatening anaphylaxis minutes after administration of a single dose of intravenous 1.2 g AMX-CL preoperatively for oocyte retrieval. No colloids or other medications were given, and there was a significant acute tryptase rise to 38.0 ng/mL from a baseline of 2.0 ng/mL. Skin and basophil activation tests were all negative to penicillin allergenic determinants, AMX and CL. Other potential culprits such as chlorhexidine and latex were also excluded. A graded oral DPT with 10 mL of AUGMENTIN SUSPENSION (GlaxoSmithKline) was also negative. Six months later, she tolerated a subsequent 1.2 g dose of intravenous AUGMENTIN (GlaxoSmithKline) without reaction. We discovered that the formulation of intravenous AMX-CL in her index reaction was produced by a different pharmaceutical company, but no excipient list was available. In Hong Kong, drugs are not required by law to include excipient lists in product inserts, and we have been unable to retrieve an excipient list despite extensive efforts. This particular formulation has also been out of stock in Hong Kong, and there is no remaining supply for analysis or skin testing.

We hope that these unfortunate and challenging cases can remind physicians of the importance of taking a complete drug allergy history and to consider possible excipient allergy especially when faced with seemingly discrepant investigation results.

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TABLE I. Example of differences in excipients among different formulations of amoxicillin-clavulanic acid

Trade name	AUGMENTIN SUSPENSION	
	457 mg/5 mL—mixed fruit flavor	AUGMENTIN ES
Amoxicillin:clavulanic acid ratio	400 mg:57 mg	600 mg:42.9 mg
Manufacturer	GlaxoSmithKline, UK	GlaxoSmithKline, UK
Product reference	GlaxoSmithKline ⁴	GlaxoSmithKline ⁵
Excipient list	Xanthan gum, hydroxypropylmethylcellulose, colloidal silica, succinic acid, silicon dioxide, raspberry, orange “1,” orange “2,” golden syrup dry flavors, aspartame	Colloidal silicon dioxide, sodium carboxymethylcellulose-12, strawberry cream flavor, xanthan gum, aspartame, silicon dioxide

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Reply



To the Editor:

We thank Li et al¹ for their comments on our recent publication.² We agree with the caution that there is a possibility of drug excipient as a culprit cause in our case. Similar to Hong Kong, drug package inserts are not enforced by law to include excipient lists in Thailand. Therefore, Thai allergists confront a similar situation in practice.

The 2 formulations in both drug provocation tests were different. We wrote letters to both pharmaceutical companies, and they replied with some data on excipients (Table I). The trade name and companies' names are not disclosed because of their internal disclosure policies. Some excipients in amoxicillin-clavulanic acid were the same in both formulations used in the 2 provocation tests, but some were not. We have identified the excipients that were different between tests in bold font. The 3 different excipients in the second provocation included apricot powder, caramel powder, and mannitol. There is a possibility that these excipients could have caused an immediate hypersensitivity reaction.^{3,4} Caramel coloring may be derived from various sources that are considered as common allergens, such as starch hydrolysates (from wheat), malt syrup (may have been derived from barley), or lactose (from milk). Our patient had no previous history of food or plant food allergy. However, he reported a history of hypersensitivity to other drugs, including clarithromycin and levofloxacin although he was unable to recall the details of these events.

We have read your interesting reports on the importance of excipient allergy in patients with immediate hypersensitivity to systemic corticosteroids.⁵ We are well aware that complete allergy testing would increase the chance of culprit(s) identification. When dealing with a complicated situation, such as perioperative hypersensitivity, the excipients and related disinfectants have been routinely included in skin test panels since 2017 in our institution.^{6,7}

TABLE I. Excipients of amoxicillin-clavulanic used in 2 drug provocation tests

	First provocation (negative)	Second provocation (positive)
Formulation	AM-CL suspension	AM-CL syrup
AM:CL ratio	200 mg:28.5 mg	600 mg:42.9 mg
Manufacturer	Company A	Company B
Product reference	Not available	Not available
Excipient list	Aspartame, colloidal silica, hydroxypropyl methylcellulose , monosodium citrate , sodium citrate , strawberry flavor , strawberry guarana flavor , xanthan gum, FD&C red "40"	Aspartame, apricot powder , caramel powder , colloidal silica, mannitol , xanthan gum

AM, Amoxicillin; CL, clavulanic acid; FD&C, Federal Food, Drug, and Cosmetic Act code.

Note: The excipients that were different between the 2 provocations are represented with bold font.

We could not specifically conclude the culprit in our case because we did not repeat skin tests and perform *in vitro* testing for clavulanic acid and other excipients, which were limited due to the patient's condition and medications. However, based on the likely trace amounts of excipients ingested, it would be unusual for any of them to cause a fatal reaction. Our reported case together with your valuable suggestion is a cautionary tale to allergists dealing with drug hypersensitivity. We do not have enough evidence to recommend a routine test including excipients at the first evaluation of the beta-lactam allergic patients. There is a lack of excipient skin test standardization, unknown cost utility, and the risk of cutaneous sensitization to excipients. In our opinion, we would perform excipient testing for certain drugs (eg, corticosteroids)⁵ and cases with clinical resensitization to different manufactured beta-lactams after delabeling. We also advocate legal regulations to include excipient lists in the package inserts as a part of drug registration, which might lead to more complete allergy histories. We very much appreciate the helpful correspondence you have provided, and we thank your team for the data provided to fulfill the knowledge of drug allergy tests to allergists worldwide.

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