

Opioid hypersensitivity is thought to be attributable to non-IgE-mediated mast cell degranulation via direct stimulation of μ -opioid receptors.⁸ Therefore, false-positive results are possible on intradermal testing, and concerns about the validity of performing in vivo skin testing has been raised.⁹ Such concerns have led some to argue about the greater adoption of drug provocation testing to avoid overdiagnosis and unnecessary avoidance of medications.¹⁰ Minimizing the chances of false-positive results, we tested our loperamide concentrations on healthy volunteers and used authoritative, published maximum nonirritating concentrations.¹

In summary, we report a unique case of loperamide anaphylaxis confirmed on intradermal testing with possible—but not confirmed—cross-sensitization to fentanyl. Loperamide anaphylaxis is a rare but potentially fatal complication of this relatively common over-the-counter drug, and physicians need to be aware of this complication. Although our patient had no pressing reasons to use opioid medications, we thought it important to establish opioid availability should he require this urgently in the future.

Acknowledgment

We thank the patient for his informed, written consent to publish this letter.

Adrian Y.S. Lee, MBBS^{*,†,‡,§}

Anthony J.F. Smith, MBBS, PhD^{*,‡}

Matthew Krummenacher, MBBS^{||}

Tiffany L. Hughes, MBBS^{*,‡}

^{*}Department of Allergy/Clinical Immunology
Flinders Medical Centre
Bedford Park, Australia

[†]Department of Immunology
SA Pathology/FMC
Bedford Park, Australia

[‡]College of Medicine and Public Health Flinders University
Bedford Park, Australia

[§]Menzies Institute for Medical Research
University of Tasmania
Hobart, Tasmania, Australia

^{||}Department of Immunology
Royal Adelaide Hospital
Adelaide, Australia
adrian.lee2@sa.gov.au

References

1. Australian and New Zealand Anaesthetic Allergy Group. ANZAAG Perioperative Anaphylaxis Investigation Guidelines 2017 [cited 2019]. <http://www.anzaag.com/anaphylaxis-management/testing-guidelines.pdf>. Accessed August 12, 2019.
2. Perez-Calderon R, Gonzalo-Garijo MA. Anaphylaxis due to loperamide. *Allergy*. 2004;59(3):369–370.
3. di Bosco AM, Grieco P, Diurno MV, Campiglia P, Novellino E, Mazzoni O. Binding site of loperamide: automated docking of loperamide in human μ - and δ -opioid receptors. *Chem Biol Drug Des*. 2008;71(4):328–335.
4. Srinivasa MR, Phelan C. Death due to anaphylactic shock after ingestion of Imodium instants (loperamide). *Allergy*. 2007;62(8):965–966.
5. Nahas O, Alary V, Chiriac AM, Philibert C, Demoly P, Hillaire-Buys D. Delayed hypersensitivity reaction to loperamide: An intriguing case report with positive challenge test. *Allergol Int*. 2017;66(1):139–140.
6. Regnard C, Twycross R, Mihalyo M, Wilcock A. Loperamide. *J Pain Symptom Manage*. 2011;42(2):319–323.
7. Parsons RL. Drug absorption in gastrointestinal disease with particular reference to malabsorption syndromes. *Clin Pharmacokinet*. 1977;2(1):45–60.
8. Blunk JA, Schmelz M, Zeck S, Skov P, Likar R, Koppert W. Opioid-induced mast cell activation and vascular responses is not mediated by μ -opioid receptors: an in vivo microdialysis study in human skin. *Anesth Analg*. 2004;98(2):364–370.
9. Nasser SM, Ewan PW. Opiate-sensitivity: clinical characteristics and the role of skin prick testing. *Clin Exp Allergy*. 2001;31(7):1014–1020.
10. Li PH, Ue KL, Wagner A, Rutkowski R, Rutkowski K. Opioid hypersensitivity: predictors of allergy and role of drug provocation testing. *J Allergy Clin Immunol Pract*. 2017;5(6):1601–1606.

Safety of intramuscular testosterone in arachis oil for boys with peanut allergy requiring pubertal induction



Sustanon is a testosterone replacement therapy used for induction of puberty in males with testosterone deficiency caused by primary hypogonadism. It contains 4 esters of the natural hormone testosterone, testosterone propionate, testosterone phenylpropionate, testosterone isocaproate, and testosterone decanoate in an oil solution. The oil solution contains arachis oil. The summary of product characteristics (SPC) of Sustanon states (in sections 4.3 and 4.4) that it is contraindicated in patients allergic to peanuts because of a risk of hypersensitivity.¹ This contraindication is despite evidence that refined peanut oil, such as that used in medicines, does not pose a risk to patients with documented peanut allergy when ingested.^{2,3} To date, there is no published evidence on the safety of refined peanut oil when injected in those with known peanut allergy. The SPC also states that Sustanon is contraindicated in patients with an allergy to soy because of the risk of cross-reactivity between peanut and soy allergens. The risk of cross-reactivity between peanut and soy is not believed to be clinically significant, and even in those with a proven peanut allergy, the avoidance of soy is not recommended without a history of clinical reactivity to soy.^{4,5}

Sustanon is in long-established use in endocrine services and is given in small, incremental starting doses to mimic natural puberty.^{6,7} In our experience it is generally well tolerated, with the only

reported incidents related to dosing errors (eg, the administration of a full 250-mg vial instead of the prescribed 50-mg initial dose).⁸ To date, there have been no published reports of anaphylaxis in patients administered Sustanon. Some reports exist for anaphylaxis to excipients other than arachis oil in different depot testosterone preparations.⁹ Anecdotally, the current SPC recommendations have naturally led to anxiety among parents of boys undergoing pubertal induction, community pharmacists, and general practitioners (who administer the depot injections) about the use of this particular testosterone formulation in peanut allergic individuals.

Other available testosterone alternatives, such as topical testosterone gel, are thought to be less appropriate given the associated risks of toxic effects, potential issues with adherence during adolescence, and the difficulty in titration of dose to appropriately mimic natural puberty's tempo in line with peers.

Our 12-year-old patient had a diagnosis of primary hypogonadism caused by bilateral congenital absent testes. He had been fully investigated as an infant for the presence of testes because he was an otherwise normally virilized male (human chorionic gonadotropin stimulation for testosterone production and laparoscopy), and a diagnosis of exclusion of vanishing testes was made. The parents were counseled on the future need for pubertal induction with testosterone from the age of approximately 12 years. Our patient was followed up by the endocrine service, and appropriate preparation for pubertal induction was undertaken. At the chronological



Figure 1. Skin prick test results. —, negative control; +, positive control; CO, crude peanut oil; PN, peanut; Testosterone, testosterone (Sustanon); RO, refined peanut oil.

age of 12 years 5 months, bone age was reported as 12 years 6 months and height as 152 cm (75th centile, within genetic target) with a weight of 40.4 kg (50th to 75th centile). Tanner staging was axillary hair stage 3, pubic hair stage 2 and genitalia stage 1. He had a right testicular prosthesis in situ. Sustanon was chosen as the clinically most appropriate form of testosterone replacement.

Before proceeding with pubertal induction, we performed a medical history review. The patient was attending a specialist allergy service with a diagnosis of peanut, egg, and milk allergies and tree nut sensitization. Regular consumption of peanut had been advised after a negative skin prick test (SPT) result to peanut (ALK-Abello, Berkshire UK) at 2 years of age; however, this was not maintained. Further peanut exposure at 2 years 9 months caused typical perioral urticaria and flushing. The SPT result at that time was 8 mm with a specific IgE level of 6.44 kU_A/L. His most recent specific IgE level was 67.4 kU_A/L in 2015, and on the day of testing, his SPT result was 7 mm (Fig. 1). In view of the stated contraindication on the SPC for Sustanon in patients with peanut allergy, his parents were concerned regarding its use in his case and asked if alternative products would be better.

His allergist performed skin prick testing with peanut, refined peanut oil (Lakeshore, Drogheda, Ireland), crude peanut oil (Bayin, Bray, Ireland), and Sustanon. Results of testing (using commercially available solutions from ALK-Abello for peanut, negative and positive controls, and undiluted refined and crude oils, as above, in prick-prick testing) were as follows: peanut, 7 mm; refined peanut oil, 0 mm; crude peanut oil, 0 mm; and Sustanon, 0 mm (Fig. 1).

The patient and both parents agreed to administration of his first dose of Sustanon at the same visit. The full recommended dose

was administered, and he was observed for 1-hour after administration. There was no objective or subjective reaction to the dose recorded. Given the successful outcome and tolerance of the product, he continues on the prescribed regimen according to the standard endocrine protocol, and expected pubertal changes have now been documented after 6 months of treatment.

To our knowledge, this is the first reported case of Sustanon use in a patient with proven peanut allergy. Given the existing medical evidence relating to the safety of peanut oil for peanut allergic individuals and this case report, we believe it is unreasonable for patients with peanut or soy allergy to be denied Sustanon treatment on the basis of their allergies alone. We advise that practitioners should proceed with the standard prescribing practices of Sustanon in children with peanut or soy allergy, without prior allergy testing. Access to allergy services is often difficult, even in well-resourced health economies. We suggest that the SPC for Sustanon and other products containing arachis oil should be altered to reflect current medical evidence, including this case report. Given the unlikely incidence of both hypogonadism and peanut allergy occurring in a sufficient number of patients, prospective studies to further support the safety profile of Sustanon are unlikely to be feasible. We suggest that publication of further case reports or a retrospective review would aid in the alteration of the SPC of products that contain arachis oil, such as Sustanon.

Acknowledgments

We thank our patient and his parents for allowing us to share his details and Ms Triona O'Sullivan, Pharmacist, Cork University Hospital, for her assistance.

Susan Harvey, MbBChBAO*

Susan M. O'Connell, MD†

Jonathan O'B. Hourihane, FRCPI*‡

*Department of Paediatrics Cork

University Hospital

Cork, Ireland

†Department of Diabetes and Endocrinology

Children's Health Ireland at Crumlin

Dublin, Ireland

‡Department of Paediatrics and Child Health

University College Cork

Ireland

jonathan.hourihane@hse.ie

References

1. eMC. Sustanon 250, 250mg/ml solution for injection: summary of product characteristics. <https://www.medicines.org.uk/emc/product/5373/smcp#>. Accessed July 3, 2019.
2. Hourihane JO'B, Bedwani SJ, Dean TP, Warner JO. Randomised, double-blind, crossover challenge study of allergenicity of peanut oils in subjects allergic to peanuts. *BMJ*. 1997;314:1084–1088.
3. McCarthy S, Murphy M, Hourihane JO'B. Peanut allergy and isotretinoin. *Clin Exp Dermatol*. 2016;41(7):814–815.
4. Sicherer SH, Sampson HA, Burks AW. Peanut and soy allergy: a clinical and therapeutic dilemma. *Allergy*. 2000;55:515–521.
5. Patel N, Vazquez-Ortiz M, Lindsley S, Campbell DE, Turner PJ. Low frequency of soya allergy in peanut-allergic children: relevance to allergen labelling on medicines. *Allergy*. 2018;73(6):1348–1350.
6. Rogol AD, Richmond EJ. Male pubertal development and the role of androgen therapy. *Nat Clin Pract Endocrinol Metab*. 2007;3(4):338–344.
7. Han TS, Bouloux MG. What is the optimal therapy for young males with hypogonadotropic hypogonadism? *Clin Endocrinol*. 2010;72:731–737.
8. Donaldson JF, Davis N, Davies JH, Rees RW, Steinbrecher HA. Priapism in teenage boys following depot testosterone. *J Pediatr Endocrinol Metab*. 2012;25(11–12):1173–1176.
9. Ong G, Somerville C, Jones T, Walsh J. Anaphylaxis triggered by benzyl benzoate in a preparation of depot testosterone undecanoate. *Case Rep Med*. 2012;2012:384054.