

Should succinate esters be considered excipients in systemic corticosteroid allergy?



To the Editor:

We read with interest the article of Li et al¹ because it confirms our previous suspicions about the undervalued role of excipients in immediate-type hypersensitivity to commercial corticosteroid formulations for systemic use.² As the study of Li et al demonstrates, a diagnostic kit to skin-test drug excipients would be strongly desirable, although it would be first necessary to establish what excipients should be investigated with skin tests. In the absence of such a kit, the allergic workup to diagnose an allergy to corticosteroids or other medications excluding the responsibility of their excipients is based on the recognition of the possible role of excipients and a “do-it-yourself” allergenic panel for skin tests.^{1,2} In their experience, Li et al consider the succinate moiety as a preservative and they include it in their algorithm, as previously suggested by Caimmi et al.³ In the literature there are case reports demonstrating that patients who have developed an immediate-type hypersensitivity to methylprednisolone sodium succinate administered intravenously may tolerate a challenge with oral pure methylprednisolone, that is, without any esterification on C21.³⁻⁶ That observation has led authors to consider the succinate moiety a potential epitope of the steroid molecule in some cases.^{3,6} However, an alternative hypothesis is also possible. From a pharmacological point of view, esterification on C21 has been introduced to increase the solubility of a steroid molecule, but a study performed by Wilkinson and English⁷ on topical hydrocortisone contact allergy provides information that could be useful in systemic corticosteroid allergy as well. In 1991 these authors performed intradermal tests with different moieties of hydrocortisone in 11 patients who had positive patch test results to tixocortol pivalate 1%. Tixocortol pivalate is almost a homolog of hydrocortisone with an –SH group on C21, and for that reason it is a good marker of contact sensitivity to hydrocortisone.⁷ These authors found that succinate, sodium phosphate, and acetate moieties have different solubilities and binding affinities for proteins, which were high for succinates, medium for sodium phosphate, and poor for acetate. Furthermore, because the C21 esterification is responsible for the steroid molecule’s protein-binding property, they argued it was irrelevant for hydrocortisone allergenicity,⁷ because C21 esterifications (succinate, sodium phosphate, acetate, or others) are quickly hydrolyzed either in skin⁸ or in liver,⁹ thus making the steroid molecule free and available for its cellular receptor.

Biochemically, the structure of hydrocortisone or cortisol is composed of 3 rings with 6 carbon atoms designated A, B, and C and 1 ring made of 5 carbon atoms designated D.⁷ Wilkinson⁷, resuming a previous study of Bundgaard, proposed that in an aqueous solution, hydrocortisone is degraded to a steroid glyoxal, that is, a steroid with an aldehyde group on C21. Such a reactive group on C21 determines the irreversible binding of steroid molecule to the guanidine groups of arginine, thus converting the steroid hapten into a complete antigen.

For that reason, the way in which methylprednisolone binds serum protein, mainly albumin,^{2,10} may change its spatial disposition and consequently its presentation to an IgE paratope in a

true allergic reaction, and, in our opinion, the high affinity of the succinate moiety to protein allows the steroid to mimic the spatial disposition of the steroid glyoxal.

A pharmacodynamic study of the way hydrocortisone and prednisolone bind serum proteins suggested that the introduction of a double bond on C1-C2 of the steroid A ring, as in prednisolone, leads to an increased affinity of the steroid molecule for serum proteins, such that prednisolone’s avidity for serum albumin is 300 times higher than that of hydrocortisone.¹⁰ That changes the conformational orientation of the steroid molecule, because in that way the ring D and C21 are oriented toward the pocket of an IgE paratope, instead of the A ring, as is the case in succinate esters. Methylprednisolone differs from prednisolone in only the introduction of a methyl group (–CH₃) on C6 of the B ring. In other words, because the A ring could be considered the “head” of the steroid molecule and the D ring the “tail,” a specific IgE antibody to methylprednisolone, presumably generated by a steroid glyoxal, is used to recognize the “head” of a steroid molecule, but it does not interact with the “tail,” when the link to carrier protein is given by the C1-C2 double bond of the A ring, allowing the tolerance of oral methylprednisolone. Consecutively, succinate salts increase the immunogenicity of the steroid molecule for steric reasons, but they are not immunogenic “per se.” They are not able to promote an IgE response toward themselves as are the other excipients, such as carboxy-methylcellulose, polyethylene glycol, or povidone,² and skin test results with pure succinates, when performed, have always been negative.^{11,12} In contrast, patients sensitized to oral methylprednisolone cannot tolerate methylprednisolone succinate because after its liver metabolism, the hydrolysis of succinate makes the molecule free to bind serum protein through the double C1-C2 bond.¹³ We would emphasize that immediate-type hypersensitivity reactions to corticosteroids are still a riddle for most of allergists because corticosteroid allergy occurs rarely,¹ and so the study on a large cohort of patients as performed by Li et al is welcome to increase our skills in that field.

Gianfranco Calogiuri, MD, PhD^a

Caterina Foti, MD, PhD^b

Eustachio Nettis, MD^c

Elisabetta Di Leo, MD, PhD^d

Luigi Macchia, MD, PhD^e

Angelo Vacca, MD, PhD^e

^aPneumology and Allergy Department, Hospital Sacro Cuore, Gallipoli, Lecce, Italy

^bDermatologic Clinic, Department of Biomedical Science and Human Oncology, University of Bari, Bari, Italy

^cDepartment of Emergency and Organ Transplantation, School of Allergology and Clinical Immunology, University of Bari, Bari, Italy

^dSection of Allergy and Clinical Immunology, Unit of Internal Medicine, “F. Miulli” Hospital, Acquaviva delle Fonti, Bari, Italy

^eDepartment of Biomedical Sciences and Human Oncology, Section of Internal Medicine, University of Bari, Bari, Italy.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication October 21, 2018; accepted for publication October 23, 2018.

Corresponding author: Gianfranco Calogiuri, MD, PhD, Via G.D’Annunzio 37, Lecce 73100, Italy. E-mail: gf.calogiuri@libero.it.

REFERENCES

1. Li PH, Wagner A, Thomas I, Watts TJ, Rutkowski R, Rutkowski K. Steroid allergy: clinical features and the importance of excipient testing in a diagnostic algorithm. *J Allergy Clin Immunol Pract* 2018;6:1655-61.

2. Calogiuri G, Garvey LH, Romita P, Macchia L, Foti C. Hypersensitivity reactions from excipients in systemic glucocorticoid formulations. *Antiinflamm Antiallergy Agents Med Chem* 2016;15:91-100.
3. Caimmi S, Caimmi P, Bousquet J, Demoly P. Succinate as opposed to glucocorticoid itself allergy. *Allergy* 2008;63:1640-3.
4. Borja JM, Galindo PA, Feo F, Gomez E. Urticaria to methylprednisolone sodium hemisuccinate. *Allergy* 2001;56:791.
5. Koutsostathis N, Vovolis V. Severe immunoglobulin E-mediated anaphylaxis to intravenous methylprednisolone succinate in a patient who tolerated oral methylprednisolone. *J Investig Allergol Clin Immunol* 2009;19:330-2.
6. Gelincik A, Yazıcı H, Emre T, Yakar F, Buyukozturk S. An Alternative approach to a renal transplant patient who experienced an immediate type systemic reaction due to methylprednisolone sodium succinate. *J Investig Allergol Clin Immunol* 2009;19:162-3.
7. Wilkinson SM, English SC. Hydrocortisone: an investigation into the nature of the allergen. *Contact Dermatitis* 1991;25:178-81.
8. Kitano Y. Hydrolysis of hydrocortisone 17-butyrate 21-propionate by cultured human keratinocytes. *Acta Derm Venereol* 1986;66:98-102.
9. Needs CJ1, Smith M, Boutagy J, Donovan S, Cosh D, McCredie M, et al. Comparison of methylprednisolone (1 g IV) with prednisolone (1 g orally) in rheumatoid arthritis: a pharmacokinetic and clinical study. *J Rheumatol* 1988;15:224-8.
10. Rocci ML Jr, D'Ambrosio R, Johnson NF, Jusko WJ. Prednisolone binding albumin and transcortin in the presence of cortisol. *Biochem Pharmacol* 1982;31:289-92.
11. Mansfield LE, Ting S, Haverly RW. Anaphylaxis caused by the sodium succinate ester of hydrocortisone and methylprednisolone. *J Asthma* 1986;23:81-3.
12. Walker AI, Rawer HC, Sieber W, Przybilla B. Immediate type hypersensitivity to succinylated corticosteroid. *Int Arch Allergy Immunol* 2011;155:86-92.
13. Compalati E, Guerra L, Rogkakou A, Zanella C, Scordamaglia A, Passalacqua G. Angioedema after administration of methylprednisolone to treat drug allergy. *Allergy* 2007;62:1346-8.

<https://doi.org/10.1016/j.jaip.2018.10.047>