

Hypersensitivity to lipoic acid

Francesco Marchi, M.D., Ph.D* and Anna Carabelli, M.D*.

*S.D. Allergologia Clinica, Azienda Ospedaliero-Universitaria Pisana, Via Roma 67, 56126 Pisa, Italy

Dear Editor,

Though we daily deal with adverse reactions to almost any kind of allergen, sometimes our job can still be surprising. We examined a 44-year-old woman with autoimmune hypothyroidism and essential hypertension, who was regularly taking Eutirox® and Triatec HCT® tablets (see table 1 for content details). A recent immediate (<60'), diffuse, self-limiting (about 2-3 hours) urticarial rash after the intake of Destior R+® (Sintactica, Italy) stood out within her allergological history. Destior R+® is an antioxidant-multivitamin product containing lipoic acid (LA, 600 mg), thiamine, pyridoxine, DL-alpha-tochopheryl acetate, lysine, lactose, carboxymethylcellulose (50 mg) (1) microcrystalline cellulose, stearate, and talc. Planning the diagnostic path, we decided to bypass the skin tests phase because of the moderate features of the adverse event and the low/uncertain sensitivity and predictive values expected. During a first challenge test (DPT) with Destior R+®, about 25 minutes after completing the whole dose, the patient developed another widespread urticarial reaction without other complaints; complete resolution was obtained with the prompt administration of antihistamines and steroids. Serum tryptase was 5.3 mcg/L, versus a basal value of 1.8 mcg/L. Since we couldn't acquire pure components of Destior R+® except carboxymethylcellulose, we decided to surrogate them with commercially available products. DPTs with pure carboxymethylcellulose (80 mg; Roquette, France), thiamine (100 mg; Benerva®, Teofarma, Italy), pyridoxine (100 mg; Benadon®, Bayer, Germany), DL-alpha-tochopheryl acetate (100 mg; Evion®, Dompé, Italy) were performed uneventfully; conversely, our patient reacted to LA (670 mg; Tiobec®, Laborest, Italy) developing another urticarial rash, easily controlled again without the need of epinephrine administration; serum tryptase was 4.2 mcg/L.

Lipoic acid, also known as thiocetic acid, is a medium length chain fatty acid deriving from caprylic (octanoic) acid by addition of two sulphur atoms to constitute a pentatomic ring (figure 1) (2). Small amounts of LA are contained in various foods. It acts principally as an antioxidant and its R (alpha) enantiomer has been proposed for the treatment of several conditions (3).

We couldn't find cases of generalized immediate reactions to LA or orally administered vitamin B1/B6/E in the scientific literature (PubMed, Google Scholar, Web of Knowledge). Allergic reactions to lipoic acid have been previously rarely described, mainly of the delayed type, both as local contact dermatitis (4,5) and in one case as a delayed skin rash due to the consumption of another LA oral supplement (6); recently, a case of contact urticaria

to LA has also been reported (7). Until now, systemic immediate reactions to LA were only generically supposed (8) or just self-reported without any evidence (9). Here, challenge tests conducted to the diagnosis of systemic immediate hypersensitivity to LA, showing once again their essential role in our clinical practice. A further DPT with pure LA was not performed because of ethical concerns: indeed, the clinical picture was clearly indicative of hypersensitivity to LA, being LA the only relevant antigen contained in any product which caused our patient an immediate urticarial reaction and not contained in the tolerated products. The rise of serum tryptase levels after LA intake suggests that the reactions occurred through mast cells activation (10).

In the end, we learnt that in case of strong suspicion of an allergic reaction to a LA-containing product, also hypersensitivity to LA must then be considered among its possible causes.

Conflict of interest

The authors have no conflicts of interest to declare.

Ethical committee

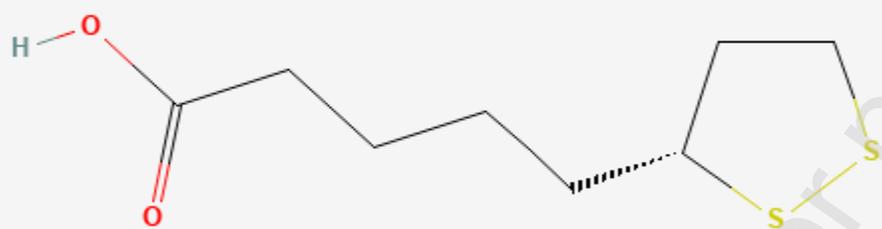
Ethical approval not necessary; written informed consent to divulge anonymously was obtained.

Acknowledgements

Many thanks to Dr. Massimiliano Borsa of Sintactica S.R.L. for sharing precious information on Destior R+®.

Table 1. Components of the aforementioned products

product	producer	components
Eutirox®	Merck	Thyroxine; corn starch, citric acid, carboxymethylcellulose, gelatine, stearate, mannitol
Triatec HCT®	Sanofi	Ramipril, hydrochlorothiazide; hydroxypropyl methylcellulose, corn starch, microcrystalline cellulose, stearyl fumarate
Destior R+®	Sintactica	Lipoic acid 600 mg, vitamin B1 as thiamine 1.1 mg, vitamin B6 as pyridoxine 1.4 mg, vitamin E as DL-alpha-tocopheryl acetate 24 mg; lysine, lactose, carboxymethylcellulose, microcrystalline cellulose, stearate, talc
Benerva®	Teofarma	Thiamine 100 mg, talc, povidone K90, stearate, methacrylate/ethyl acrylate copolymer, macrogol 6000, carboxymethylcellulose
Benadon®	Bayer	Pyridoxine 100 mg, povidone K90, talc, stearate, methacrylate/ethyl acrylate copolymer, macrogol 6000, carboxymethylcellulose
Evion®	Dompé	DL- α -tocopheryl acetate 100 mg, sucrose, isomalt, corn starch, skimmed milk, talc, arabic gum, orange flavour, titanium dioxide, red iron oxide, stearate
Tiobec®	Laborest	Alpha-lipoic acid 800 mg, microcrystalline cellulose, dicalcium phosphate, silicon dioxide, talc, stearate, carboxymethylcellulose, glyceryl behenate, hydroxy-propyl methylcellulose, polyvinylpyrrolidone, shellac, microcrystalline cellulose, stearic acid, fatty acids mono- and acetate diglycerides, titanium dioxide



Manuscript accepted for publication

References

1. courtesy of Sintactica S.R.L.
2. <https://pubchem.ncbi.nlm.nih.gov/compound/Lipoic-acid>
3. Tibullo D, Li Volti G, Giallongo C, Grasso S, Tomassoni D, Anfuso CD, Lupo G, Amenta F, Avola R, Bramanti V. Biochemical and clinical relevance of alpha lipoic acid: antioxidant and anti-inflammatory activity, molecular pathways and therapeutic potential. *Inflamm Res*. 2017 Nov;66(11):947-959. doi: 10.1007/s00011-017-1079-6
4. Bergqvist-Karlsson A, Thelin I, Bergendorff O. Contact dermatitis to alpha-lipoic acid in an anti-wrinkle cream. *Contact Dermatitis* 2006 Jul;55(1):56-7. doi: 10.1111/j.0105-1873.2006.0847c.x
5. Leysen J, Aerts O. Further evidence of thioctic acid (α -lipoic acid) being a strong cosmetic sensitizer. *Contact Dermatitis* 2016 Mar;74(3):182-4. doi: 10.1111/cod.12472
6. Rizzi A, Nucera E, Buonomo A, Schiavino D. Delayed hypersensitivity to α -lipoic acid: look at dietary supplements. *Contact Dermatitis* 2015 Jul;73(1):62-3. doi: 10.1111/cod.12393
7. Velasco-Amador JP, Prados-Carmona Á, Navarro-Triviño FJ. Contact urticaria syndrome caused by alpha-lipoic acid in a master formula for vulvar lichen sclerosus. *Contact Dermatitis* 2023 Aug;89(2):136-137. doi: 10.1111/cod.14353
8. Ziegler D. Thioctic acid for patients with symptomatic diabetic polyneuropathy: a critical review. *Treat Endocrinol*. 2004;3(3):173-89. doi: 10.2165/00024677-200403030-00005
9. Gatti M, Ippoliti I, Poluzzi E, Antonazzo IC, Moro PA, Moretti U, et al. Assessment of adverse reactions to α -lipoic acid containing dietary supplements through spontaneous reporting systems. *Clin Nutr*. 2021 Mar;40(3):1176-1185. doi: 10.1016/j.clnu.2020.07.028
10. Valent P, Akin C, Arock M, Brockow K, Butterfield JH, Carter MC, et al. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. *Int Arch Allergy Immunol*. 2012;157(3):215–25. doi: 10.1159/000328760