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CASE REPORT

Immediate allergic reaction to thiocolchicoside confirmed by skin testing and basophil activation test: A case report and literature review

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Abstract

Background: Thiocolchicoside is a muscle relaxant, anti-inflammatory, and analgesic. Administered orally, intramuscularly, or topically, this drug is used in the symptomatic treatment of muscular spasms and rheumatologic disorders. Despite its extensive use, thiocolchicoside is a very rare sensitizer.

Objective: To evaluate IgE-mediated reaction to thiocolchicoside by basophil activation test.

Methods: Allergological work-up with skin prick tests, intradermal tests and basophil activation test with thiocolchicoside.

Results: We report the first case of immediate reaction to thiocolchicoside confirmed by basophil activation test in addition to positive skin tests.

Conclusions: BAT can be considered a complementary diagnostic tool to demonstrate an IgE-mediated reaction also for muscle relaxant drugs.

Key words: Thiocolchicoside; drug hypersensitivity; basophil activation test; immediate allergic reaction; CD63+ basophils; central muscle relaxant.

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Abbreviations:

THC	Thiocolchicoside
GABA	γ-aminobutyric acid
BAT	basophil activation test
NSAIDs	nonsteroidal anti-inflammatory drugs
SPTs	skin prick tests
IDTs	intradermal tests
fMLP	N-Formylmethionyl-leucyl-phenylalanine

Background

Thiocolchicoside (THC) is a semisynthetic sulfur derivative of colchicoside, which has been shown to interact with γ-aminobutyric acid (GABA) - ergic and glycinergic receptors.[1]

THC is a muscle relaxant agent with anti-inflammatory and analgesic actions. It is also used topically for the treatment of muscular spasms and for rheumatologic, orthopedic and traumatologic disorders. THC is usually well tolerated, but it may occasionally cause adverse effects such as gastrointestinal symptoms, seizures, psychiatric events and, rarely, anaphylaxis.[2-4]

The basophil activation test (BAT) upon the expression of CD63 is an additional tool in the diagnosis of drug allergy that is safer than a provocation test and, in some instances, is the only available diagnostic tool.[5]

Case report

We report the first case of immediate reaction to THC confirmed by BAT in addition to positive skin tests.

A 59-year old woman (158 cm, 72 Kg) experienced a systemic reaction, characterized by generalized urticaria, labial angioedema and throat constriction, without bronchospasm or shock (grade 2 of Sampson's score of anaphylaxis), 15 minutes after intramuscular administration of diclofenac (Voltaren®, 75 mg/3 ml) and thiocolchicoside (Miotens®, 4 mg/2 ml).

She was treated in Emergency Department with intravenous corticosteroids (Metilprednisolone, Urbason®, 80 mg) and intramuscular antihistamine (Chlorpheniramine, Trimeton®, 10 mg/ml) and she was discharged at home after 24 h with oral corticosteroid prescription (Metilprednisolone, Medrol®, 16 mg twice daily for 3 days, then gradual downward titration, halving the dose every 3 days).

Her medical history included ulcerative colitis and rheumatoid arthritis treated with mesalazine, etanercept and methotrexate and occasionally with nonsteroidal anti-inflammatory drugs (NSAIDs). The patient had no known allergies.

She was referred to our Allergy Unit. An allergological work-up, including skin prick tests (SPTs), intradermal tests (IDTs), BAT with diclofenac and THC, was timed for 6 weeks after reaction to minimize the risk of false-negative results after receiving patient's written consent. SPTs were performed with undiluted diclofenac (25 mg/ml) and thiocolchicoside (2 mg/ml) with saline as the only excipient. After 20 minutes, we observed a positive reaction to THC (mean wheal 20 mm) [**Figure 1**].

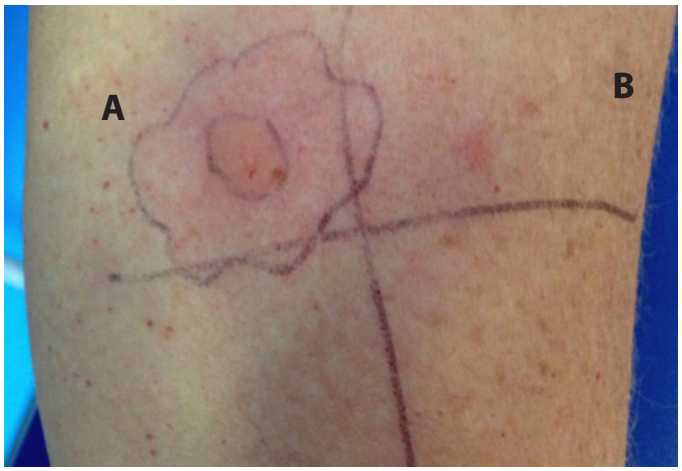

Figure 1.

IDTs were performed with diluted drugs starting from 0.0002 mg/ml for THC solution and 0.025 mg/ml for diclofenac solution. We recorded a positive area (mean wheal 9 mm) for THC 20' after performing the first IDT (0.0002 mg/ml).

SPT (25 mg/ml) and IDT (0.025-25 mg/ml) with diclofenac were negative.

Histamine (10 mg/ml) and saline were used as positive and negative controls, respectively. IDTs with THC were also performed with negative results in 10 healthy controls, after written informed consent, excluding an irritative reaction to this molecule.

SPTs were performed and read according to the indications of the European Academy of Allergy and Clinical Immunology.[5]

A drug provocation test (DPT) with THC was not performed because of the severity of the index reactions (grade 2 of Sampson's score of anaphylaxis). Furthermore, a DPT with alternative NSAIDs was not performed because, after the anaphylaxis episode, the patient independently took diclofenac by intramuscular route without adverse reactions and reported tolerating meloxicam, orally administered, for arthralgias due to her rheumatoid arthritis.

Taking into account the positive results of skin tests, BAT[6] was performed with commercially available Flow CAST thiocolchicoside kit according to the manufacturer's instructions (Buhlmann Laboratories AG, Schonenbuch, Switzerland). The Flow CAST determines the basophil activation by measuring the relative amount of CD63+ basophils within the total population of CCR3+ basophils in whole blood. The reagent contains a mixture of monoclonal antibodies to human CD63 labeled with fluorescein isothiocyanate (anti-CD63-FITC) and to human chemokine receptor CCR3 labeled with phycoerythrin (anti-CCR3-PE). As positive control, highly specific monoclonal antibody binding to the unspecific cell activator N-Formylmethionyl-leucyl-phenylalanine (fMLP) was used. The specimen of whole blood of our patient was tested for BAT with THC at different concentrations (dilutions 1/10, 1/100, 1/1000) starting from the pure solution for infusion (2 mg/ml). After preliminary dose-finding experiments, the drug concentrations, able to optimally stimulate basophils without cytotoxic effects,[7] were 0.4, 0.04 and 0.004 mg/ml. Results of BAT are expressed as the percentage of CD63+ basophils. Results of the test are considered as positive when the difference within activated basophils of the patient with and without allergen (negative control) is ≥ 5%. Results of BATs with THC are shown in **Figure 2**. Basophil activation in the patient was observed at two concentrations (12% at 0.04 mg/ml and 6% at 0.004 mg/ml), while all controls were negative [**Figure 2**].

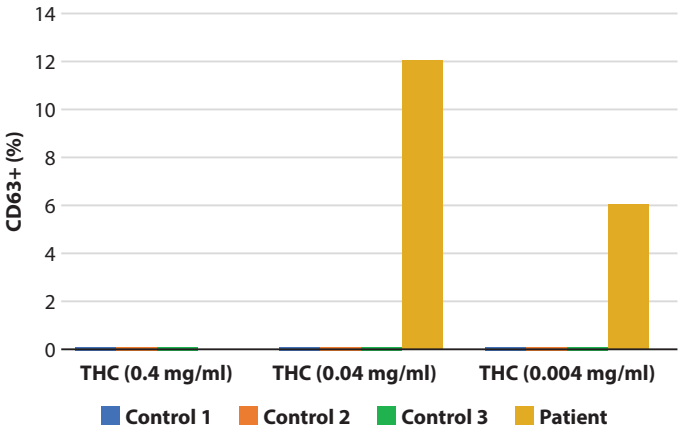

Figure 2.

Discussion

THC is a natural glycoside with centrally acting skeletal muscle relaxant effects.[8] It is an antagonist of GABA receptor function in the central nervous system.[8] Moreover, it has an agonistic action at the spinal-strychnine-sensitive receptors that can mediate its myorelaxant effect.[8] Because it is less sedating than other centrally acting muscle relaxants and has anti-inflammatory and analgesic actions, THC is commonly used in the treatment of acute muscle spasms and contractures and also in chronic osteoarticular, rheumatic, and neurologic disorders.[8,9]

THC belongs to the subgroup of spasmolytics, one of the two main groups of drugs referred as skeletal muscle relaxants.[10] Skeletal muscle relaxants are structurally distinct drugs prescribed for reducing muscle spasms, pain, and hyperreflexia. They are classified into two main groups: neuromuscular blockers and spasmolytics.[10] Spasmolytics are usually referred as centrally acting muscle relaxants given by oral route, are of two types namely, anti spasmodic and anti spasticity agents. Site of action of antispasticity agents are on the spinal cord to reduce the muscle tone due to upper motor neuron lesions in the spastic neurological conditions. Baclofen, eperisone, tolperisone and THC are the commonly used anti spastic agents. Furthermore, drugs like diazepam and tizanidine are approved as anti spasmodic - anti spastic agents.[11]

In literature, documented hypersensitivity reactions to THC are uncommon, despite of the extensive use of the drug.[1] The few published cases include: Embolia cutis medicamentosa (or Nicolau syndrome),[12] immediate and delayed contact dermatitis,[13,14] photosensitivity reactions[15] and four cases of immediate anaphylaxis after administration of THC.[3] In these reports, an IgE-mediated reaction to THC is demonstrated exclusively by positive skin test results (SPTs and IDTs).

To our knowledge, we reported the first case of immediate reaction to THC confirmed by BAT in addition to positive skin tests.

In order to explore if BAT could be a functional in vitro test for the diagnosis of immediate-type drug hypersensitivity also to other centrally acting muscle relaxants, a review of literature was carried out. Pubmed and Web of science were searched up to March 2020.

Primary screening was performed using the following MeSH headings and keywords: "skeletal muscle relaxants", "muscle relaxants, central", "centrally acting muscle relaxants", "baclofen", "eperisone", "tolperisone", "inaperisone", "lanperisone", "silperisone", "diazepam" and "tizanidine". Secondary screening was performed using terms such as "drug hypersensitivity", "drug hypersensitivity, immediate" and "anaphylaxis". Tertiary screening for identifying cases of IgE mediated hypersensitivity to before mentioned drugs. Only English language reports were included. From each report, we retrieved data regarding culprit drug, age, sex, clinical manifestations and allergological diagnostic tests (SPTs, IDTs, drug provocation test and BAT). The selected relevant papers are summarized in **Table 1**.

No study reports IgE-mediated reactions to baclofen, a GABA derivative that is a specific agonist of GABA-B receptors, used in the treatment of muscle spasticity, especially that due to spinal cord injuries.

More data are available about the IgE-mediated reactions to propiophenones with properties of central muscle relaxants (eperisone, inaperisone, lanperisone, silperisone and tolperisone). Recently, Shin B. and co-workers investigated the clinical manifestations of eperisone-induced immediate-type hypersensitivity and evaluated the role of IDT. The Researchers retrospectively reviewed medical records from 23 patients diagnosed as eperisone-induced immediate-type hypersensitivity with certain or probable causality. Immediate-type hypersensitivity reactions to eperisone, confirmed by IDT and/or DPT, occurred in 17 patients.[16] In the same year, Park K.H. et al. reviewed eperisone-related pharmacovigilance data reported in Korea from 2010 to 2015. Moreover, 7-year data reported in a single center were also reviewed. In the single center study, there were 11 patients with eperisone-induced anaphylaxis. All the patients underwent DPT and all the provoked patients showed a positive reaction. Four of the 11 patients with anaphylaxis also underwent SPT and BAT, which were all negative.[17] Previously, Miki Y. et al. reported a case of eperisone-induced anaphylaxis, in which SPT and BAT were negative. An oral challenge test was necessary to diagnose eperisone-induced acute hypersensitivity.[18] Even before, in 2012, Hur G.Y. and colleagues described three allergic reactions caused by eperisone and afloqualone. An open-label oral challenge test was performed with each drug to confirm which drugs caused the systemic reactions. To confirm the diagnosis, SPTs, IDT and BAT were performed.[19] No study reports IgE-mediated reactions to inaperisone, lanperisone and silperisone. Finally, there are few reports of hypersensitivity due to tolperisone. The first case was described by Aleksandrov in 1974. In 2003, Ribi C. et al. described four patients with anaphylaxis attributed to the intake of tolperisone hydrochloride.[20] In the same year, Kwasniewski et al. described the first case in Poland of anaphylactic shock caused by tolperisone. More recently, Glück J. et al. reported another case of anaphylaxis due to tolperisone confirmed by DPT.[21]

Diazepam, a member of benzodiazepines used since the 1960s for sedation, anterograde amnesia, anxiolysis, as well as treatment of seizures and drug-associated agitation, is a spasmolytic drug with action on central nervous system. In 1977, what was considered to be the first true anaphylaxis to diazepam was published in the British Medical Journal.[22] The mechanism was attributed to a common metabolite, desmethyldiazepam, the antigenic moiety for cross-allergenicity in benzodiazepines.[22] A recent review on published reports involving anaphylactic or anaphylactoid reactions to benzodiazepines highlights the diagnostic challenge of allergy to benzodiazepines.[23] In fact, although challenge testing remains the gold standard for diagnosis, it is not routinely performed. In 2002, Asero R. reported a case of diazepam allergy: a healthy 28-year-old nurse with no significant past medical history or allergies presenting for gastroscopy. The patient showed signs of generalized urticaria and shock requiring treatment.[24]

Tizanidine, a congener of clonidine, is a myotonolytic agent FDA-approved for the management of spasticity.[25] We did not find in the literature any cases of hypersensitivity to tizanidine.

Table 1. Immediate hypersensitivity to centrally acting muscle relaxants

Drug	Author (Reference)	Country	N° of patients [certain/ probable]	Age (yr)	Gender	Allergic hystory	Clinical manifestations	SPT [concentration of culprit drug]	IDT	DPT	BAT
Thiocolchicoside	Nucera E. et al.	Italy	1	54	F	Neg	Anaphylaxis	Pos [2 mg/ml]	Pos [0.0002 mg/ml]	ND	Pos [0.04 and 0.004 mg/ml]
	Caimmi D. et al.[2]	Italy, France	1	29	F	Previous atopic dermatitis and asymtomatic sensitization to house dust mites.	1st: generalized urticaria. 2nd: anaphylaxis.	Pos [2 mg/ml]	ND	ND	ND
	Brosseron L. et al.[3]	Portugal	1	67	F	Non-allergic asthma.	Anaphylaxis.	Pos [2 mg/ml]	ND	ND	Refused by the patient.
	Amaral L. et al.[4]	Portugal	2	1st pt: 56 2nd pt: 52	1st pt: F 2nd pt: M	Neg	Anaphylaxis.	1st pt: Neg 2nd pt: Neg	1st pt: pos [2 mg/ml] 2nd pt: pos [2 mg/ml]	ND	ND
	Mancuso G.[14]	Italy	1	27	F	Nickel contact allergy.	Itching.	Pos [0.25% aq.]	ND	ND	ND
Eperisone	Shin B. et al.[16]	Korea	23 [17/6]	45 [mean]	6/17 (M/F)	35% of sample.	Cutaneous : 100% of sample. Gastrointestinal : 65% of sample. Respiratory : 57% of sample. Cardiovascular : 39% of sample. Anaphylaxis: 100% of sample.	Pos 5/23 pts [NP]	Pos 5/9 pts [NP]	14/14 pts	ND
	Park K.H. et al.[17]	Korea	37 [12/25]	57 [mean]	13/24 (M/F)	Unknown.	11 pts: anaphylaxis.	Neg 4/4	ND	Pos 11/11	Neg 4/4 [1, 0.1, 0.01 and 0.001 mg/mL]
	Miki Y. et al.[18]	Japan	1	64	F	Bronchial asthma.	Anaphylaxis.	Neg	ND	Pos	Neg
	Hur G.Y. et al.[19]	Korea	3	1st pt: 54 2nd pt: 62	F	Neg	Anaphylaxis.	Neg	Neg	Pos	ND
Tolperisone	Ribi C. et al.[20]	Switzerland	4	1st pt: 45 2nd pt: 59 3rd pt: 48 4th pt: 55	F	1st pt: unknown. 2nd pt: allergy to penicillin. 3rd pt: allergic rhinitis and asthma. 4th pt: chronic rhinitis.	Anaphylaxis.	Neg 1/1	ND	ND	ND
	Gluck J. et al.[21]	Poland	1	57	M	Unknown.	Pruritus, erythema and facial edema	Neg	Neg	Pos	ND
Diazepam	Asero R.[24]	Italy	1	28	F	Neg	Anaphylaxis.	Pos [5 mg/ml]	Pos [5 mg/ml]	ND	ND

M: male; F: female; SPT: skin prick test; IDT: intradermal tests; DPT: drug provocation test; BAT: basophil activation test; ND: not done; Neg: negative reaction; Pos: positive reaction; NP: not provided.

The not negligible number of reported cases of immediate-type drug hypersensitivity to centrally acting muscle relaxants, properly diagnosed and detailed in **Table 1**, highlights: 1) the high prevalence of the phenomenon in the female population, 2) the severity of reaction to culprit drug (anaphylaxis is frequently reported), and, 3) the heterogeneity of allergological work-up, partly influenced by clinical history and severity of the reaction (BAT was reported only in three reports).

According to a recent review,[6] BAT have promising results in immediate hypersensitivity reactions to several classes of drugs such as pyrazolones, neuromuscular blockers, beta-lactams and platinum compounds, all examples of classical IgE-mediated hypersensitivity drug reactions, while its usefulness is lower for NSAIDs and quinolones, that degranulate mast cells through non-IgE-mediated mechanism.

Our case demonstrates that BAT can be considered a valid diagnostic tool to investigate an IgE-mediated reaction also for muscle relaxant drugs especially for patients who experienced severe reactions and when the diagnosis cannot be established by serum-specific IgE.

In summary, the combination of multiple methods, such as skin tests and BAT, could improve the diagnostic accuracy for THC-induced anaphylaxis. Although further studies should be performed to accumulate evidence showing the effectiveness of BAT, our case represents the first experience focused on the possible role of BAT to get the diagnosis of hypersensitivity reactions to muscle relaxant drugs, with the advantage of safety for patient avoiding provocation test.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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