

Conjunctival Provocation Test for the Diagnosis of Ocular Hypersensitivity to Chlorobutanol

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Purpose: Conjunctival provocation test (CPT) is a useful tool for the determination of the reagent in patients with allergic conjunctivitis. Our aim is to present an unusual reaction of ocular hypersensitivity to chlorobutanol by using this technique.

Methods: This case describes a 56-year-old woman who presented intense ocular pruritus and conjunctival hyperemia with each instillation of Colircusi Fluotest (Alcon, El Masnou, Spain). Skin tests and CPTs were considered.

Results: Skin tests were all negative. CPTs were performed with commercially available ophthalmic products that were selected for their compositions. Chlorobutanol was presumed as the reagent through elimination. Positive CPT with purified chlorobutanol confirmed this hypothesis.

Conclusion: CPT performed with commercially available products can be a useful, accessible, and inexpensive technique to orient the diagnosis of suspected ocular hypersensitivity to a pharmacologic component. To our knowledge, this is the first report of ocular hypersensitivity to chlorobutanol.

Key Words: chlorobutanol, hypersensitivity, excipient, conjunctival provocation test, conjunctival allergen challenge

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Fluorescein with topical anesthetic instillation is performed in the daily ophthalmic practice for multiple diagnostic purposes. The most widespread combination in Spain is Colircusi Fluotest (Alcon, El Masnou, Spain) (Table 1). We

present an unusual case of ocular hypersensitivity to this compound and the diagnostic process to elucidate the exact causative component.

CASE REPORT

A 56-year-old woman came to our clinic complaining of intense ocular pruritus and conjunctival hyperemia approximately 1 minute after each instillation of Colircusi Fluotest (Fig. 1A). This response appeared 1 month before, and the patient had previously tolerated this formulation well. Itching and redness were well controlled with Maxidex (Alcon, Ft. Worth, TX) (Table 1).

The patient used Xalatan (Pfizer, New York, NY) for bilateral chronic open-angle glaucoma for 2 years without any ocular reaction (Table 1). Otherwise, she has no previous history of other medical problems.

It was decided that skin tests should be carried out because an allergic entity was suspected. Patch tests with the European standard series (23 allergens), local anesthetics, benzalkonium chloride, Colircusi Fluotest, and Xalatan were all negative after 48 and 96 hours. In addition, a prick test with Colircusi Fluotest produced no response.

Because of the circumstantial unavailability of preservative-free allergen solutions of the single components of Colircusi Fluotest, a conjunctival provocation test (CPT) was performed with commercial products that were selected for their compositions (Table 1).

Day 1

There was a positive reaction to Colircusi Anestesico Doble (Alcon, El Masnou, Spain) and negative reaction to Colircusi Fluoresceina (Alcon, El Masnou, Spain) (Fig. 1B). Fluorescein was excluded as the causative agent. An allergic reaction to either the topical anesthetic or excipient that both Colircusi Fluotest and Colircusi Anestesico Doble contained was suspected.

Day 2

There was a negative reaction to both Prescaina 0.4% (Llorens, Barcelona, Spain) and Anestesico Braun 1% S/A (Braun, Rubi, Spain), which was half-diluted to obtain the same tetracaine concentration as in Colircusi Anestesico Doble (Fig. 1C). The association of local anesthetics with hyperacute conjunctivitis was excluded. The excipient was probably the responsible allergen through elimination.

Day 3

There was a positive reaction to Colircusi Deicol (Alcon, El Masnou, Spain) eye drops and to Tobrex (Alcon, Fort Worth, TX)

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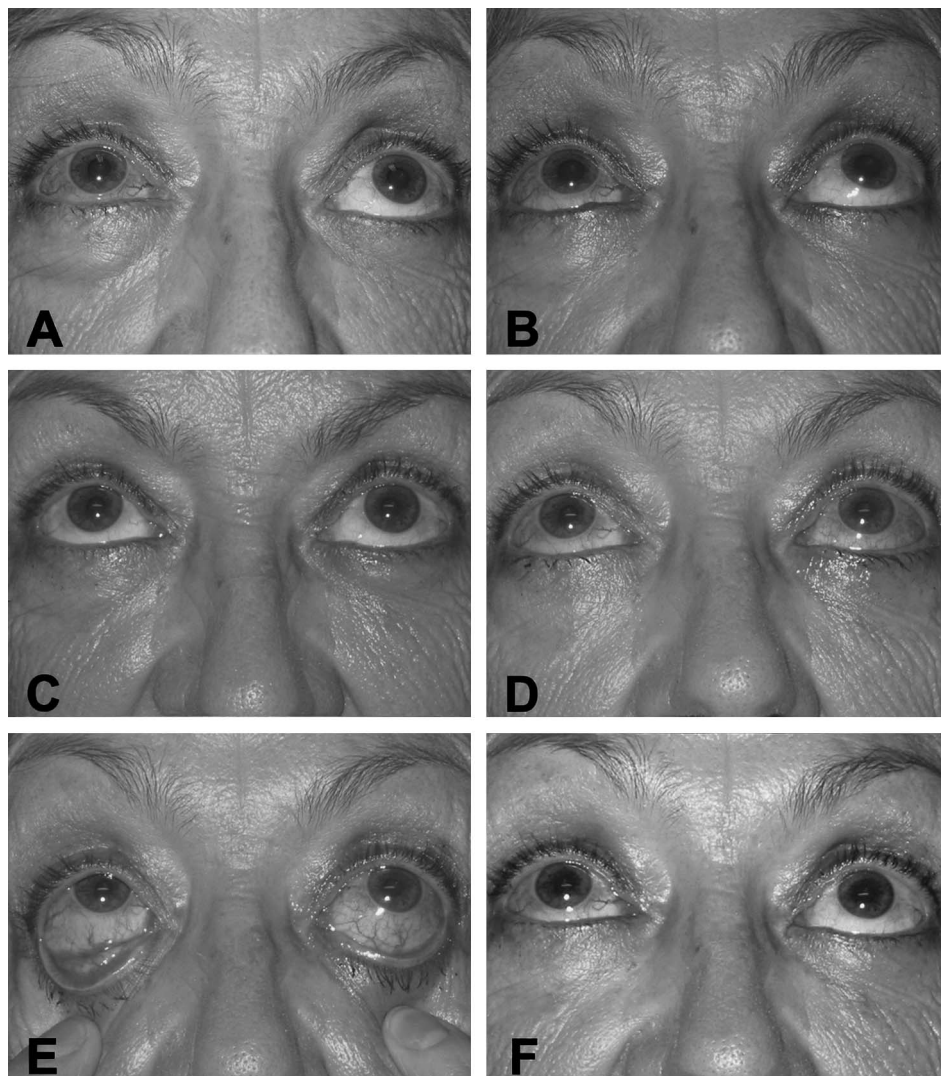


FIGURE 1. CPTs. Colircusi Fluotest in the right eye and saline in the left eye (A); Colircusi Anestésico Doble in the right eye and Colircusi Fluoresceína in the left eye (B); Prescaina 0.4% in the right eye and half-diluted Anestésico Braun 1% S/A in the left eye (C); Colircusi Deicol in the right eye and Tobrex ophthalmic ointment in the left eye (D and E); and Chlorobutanol 0.05% in the right eye and saline in the left eye (F). For the exact compositions of the different products, see Table 1.

ophthalmic ointment (Figs. 1D, E). It was therefore presumed that chlorobutanol was the reagent.

Day 4

Finally, a preparation of purified chlorobutanol 0.05% was obtained through the Pharmacy Department of the Doctor Peset University Hospital. A positive reaction to this preparation confirmed our hypothesis (Fig. 1F).

Each day, the same products were instilled for at least 7 more control patients. No ocular reaction took place, so an irritant mechanism was excluded.

No further recurrence of the symptoms was observed in the patient when Prescaina 0.4% was combined with Colircusi Fluoresceína for ophthalmic exploration for up to 7 months of follow-up.

DISCUSSION

CPT is a highly allergen-specific and sensitive tool, which is especially useful in patients with negative skin

tests and a positive clinical history of allergic ocular disease to assess the specific, local response of the conjunctiva.¹

However, the limits of CPTs are essentially related to the scarce availability and high costs of water-soluble preservative-free allergens. When an allergy to a pharmacologic compound is suspected, it was considered that CPT performed with commercially available products (selected for their compositions) could be a useful, accessible, and inexpensive technique for diagnosis, as seen in this case.

Chlorobutanol is widely used as a safe preservative² not only in ocular dyes (Colircusi Fluotest, Fluress, and Fluor-I-Strip) but also in other ophthalmic (Table 2) and nonophthalmic preparations worldwide.

Although hypersensitivity reactions to chlorobutanol in parenteral use^{3,4} or nasal sprays⁵ have been observed, to our knowledge, no previous reports of acute conjunctival hypersensitivity to chlorobutanol in the eye from topical use exist.

TABLE 1. Composition and Ocular Reaction of the Different Compounds Used in the Patient

Trade Name	Composition	Reaction
Maxidex	Dexamethasone (0.1%)	—
	Benzalkonium chloride (0.01%)	
Xalatan	Latanoprost (0.005%)	—
	Benzalkonium chloride (0.02%)	
Colircusi Fluotest	Sodium fluorescein (0.25%)	+
	Oxybuprocaine hydrochloride (0.4%)	
	Boric acid (1.31%)	
	Chlorobutanol (0.1%)	
Colircusi Anestésico Doble	Naphazoline hydrochloride (0.05%)	+
	Oxybuprocaine hydrochloride (0.4%)	
	Tetracaine hydrochloride (0.5%)	
	Chlorobutanol (0.05%)	
Colircusi Fluoresceína 2%	Sodium fluorescein (2%)	—
	Thiomersal (0.005%)	
Prescaina 0.4%	Oxybuprocaine hydrochloride (0.4%)	—
	Boric acid (1%)	
	Mercury (0.1%)	
Anestésico Braun S/A 1%	Tetracaine hydrochloride (1%)	—
	Benzoic acid (0.1%)	
Colircusi-Deicol	Dexamethasone phosphate (0.1%)	+
	Chloramphenicol (0.73%)	
	Chlorobutanol (0.5%)	
	Thiomersal (0.01%)	
Tobrex ophthalmic ointment	Tobramycin (0.3%)	+
	Chlorobutanol (0.5%)	

TABLE 2. Alphabetical List of Ophthalmic Compounds Containing Chlorobutanol as an Excipient

Atropine Sulfate Ophthalmic Ointment (Fougera, Melville, NY; Allergan, Irving, CA)	Lacril 0.5% (Allergan, Markham, Canada)
Baciguent (Pharmacia & Upjohn, Mississauga, Canada)	Lacrilube ointment (Allergan, Irving, CA)
Biamotil-D (Allergan-Frumtost, Sao Paulo, Brazil)	Lacrimol (Allergan, Ettlingen, Germany)
Blink-N-Clean For Contact Lens (Allergan, Irving, CA)	Liquifilm (Allergan, Irving, CA)
Bro-Lac (3m Pharmaceuticals, St. Paul, MN)	Lyophrin Diluent (Alcon, Ft. Worth, TX)
Celestone (Schering-Plough, Madrid, Spain)	Mycitracin (Upjohn, Rydalmere, Australia)
Chloroptic Celluvise 1% (Allergan, Irving, CA)	Neo-Cortef 0.5% (Pharmacia & Upjohn, Mississauga, Canada)
Coliquifilm (Allergan, Ettlingen, Germany)	Neo-Deltef (Upjohn, New York, NY)
Colircusi Anestésico Doble (Alcon, El Masnou, Spain)	Neo-Medrol (Pharmacia & Upjohn, Mississauga, Canada)
Colircusi Deicol (Alcon, El Masnou, Spain)	Nepodex (Latinofarma, Sao Paulo, Brazil)
Colircusi Fluotest (Alcon, El Masnou, Spain; Alcon, Lisboa, Portugal)	Ocudrop (Del Pharmaceuticals, Uniondale, NY)
Colirio Helios (Windson, Sao Paulo, Brazil)	Optal (Olan-Kemed, Bangkok, Thailand)
Combiamid (Winzer, Olching, Germany)	Optef (Upjohn, New York, NY)
Dexamyltrex Augensalbe (Mann, Berlin, Germany)	Optosulfex (Charton Laboratories, Mirabel, Canada)
Fluor-I-Strip -A.T. (Bausch & Lomb, Rochester, NY)	Optrex (Pierre Fabre Sante, Boulogne France)
Fluress (Akorn, Buffalo Grove, IL; Abigo, Askim, Sweden; AMO, Pymble, Australia; Allergan, Markham, Canada; Barnes-Hind, Sunnyvale, CA)	Pan-Ophthal (Winzer, Olching, Germany)
Gentamyltrex (Mann, Berlin, Germany)	Pred-G (Allergan, Irving, CA)
Kombi Stulln N (Pharma Stulln, Stulln, Germany)	Puralube (Fougera, Melville, NY)
	Tears Plus (Allergan, Irving, CA)
	Terracortril (Pfizer, Sollentuna, Sweden)
	Tobradex ointment (Alcon, Ft. Worth, TX)
	Tobrex ophthalmic ointment (Alcon, Ft. Worth, TX)
	Vitafluid Augentropfen (Mann, Berlin, Germany)

List is from a February 2006 search of Micromedex and other internet databases.

This rare reaction may be avoided by using chlorobutanol-free eye drops in sensitized subjects.

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