

Reliability of diagnostic tests for contact allergy to mydriatic eyedrops

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Adverse reactions due to the administration of mydriatic eyedrops are not uncommon. In Spain, the most commonly used are phenylephrine, tropicamide and cyclopentolate hydrochloride. In this study, 37 patients with adverse reactions to the administration of mydriatic eyedrops were investigated from January 1993 to June 1997. The aim was to assess the reliability of the diagnostic methods used, particularly the adequate concentration of allergens and the introduction of conjunctival challenge as a safe and accurate diagnostic tool in those patients who could not be diagnosed by other methods. Phenylephrine was the drug most frequently causing sensitization (93.5%) among the 31 allergic patients. Preservatives were the cause in only 1. Patch testing detected allergy in 68.5% of the subjects. 2 concentrations (1% and 10%) and vehicles (pet. and aq.) were used for phenylephrine. The most reliable was 10% aq. Reading at D4 was more useful than at D2. The sensitivity of the patch test was low (72.4%) and its negative predictive value (NPV) poor (42%). In 24% of patients, allergy to phenylephrine was detected only by conjunctival challenge test. This diagnostic method is safe and helpful and has not previously been used to diagnose adverse reactions due to mydriatic eyedrops.

Key words: mydriatic eyedrops; phenylephrine; tropicamide; preservatives; contact allergy; patch testing technique; conjunctival challenge; sensitivity; specificity; false-negative; medicaments; ophthalmics. © Munksgaard, 1998.

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Mydriatics are continually used by ophthalmologists as a tool for diagnosis (retinal exploration, refraction tests) and treatment (inflammatory diseases of anterior uveal tract). Some of them have more frequently been related to contact allergy reactions. This is true of atropine and phenylephrine. The current study was focused on evaluating reactions due to phenylephrine, since it is the most commonly used, as well as tropicamide, which is simultaneously administered with it.

Phenylephrine is a direct sympathomimetic drug, which acts on alpha-adrenergic receptors. Tropicamide has an anticholinergic action and contributes to the mydriatic power of phenylephrine due to its mydriatic and cycloplegic properties. Adverse reactions related to phenylephrine include blurred vision, burning or stinging, lacrimation, conjunctival irritation, liberation of iris pigment into the anterior chamber, corneal oedema and hypertensive crises. Reactions to tropicamide include visual hallucinations, blurred vision, confusion, mouth dryness, tachycardia, headache, in-

creased intraocular pressure and parasympathetic effects. In addition to its use in eyedrops, phenylephrine is also present in ear drops, because of its decongestant effect, and in phlebological and anti-haemorrhoidal ointments.

Although the sensitizing potential of phenylephrine is well-known, the correct concentration and vehicle for patch testing with it is not so well established. It is necessary to determine the allergic origin and identify the etiologic agent when an adverse reaction occurs after administration of mydriatic eyedrops. Most patients receiving these drugs, due to underlying disease, take the risk of periodical exposure to them. They can also be treated with them during eye surgery, in which case the amounts used are greater.

Materials and Methods

Subjects

37 patients referred from the ophthalmology department for investigation of their reactions (acute

conjunctivitis) after administration of mydriatic eyedrops were evaluated. The study was carried out from January 1993 to June 1997.

Clinical questionnaire

This took into account: age, sex, reason for ophthalmologic assessment, number of previous exposures and reactions related to them, latency of outbreak, eyedrops involved, conjunctival symptoms and involvement of the eyelids.

Patch tests

Patch tests were applied to the skin of the back for 2 days using the Al-test[®] method and Scanpor[®] tape. Readings were done at 2 and 4 days and reactions were scored as recommended by the International Contact Dermatitis Research Group. Substances used were the eyedrops indicated by the questionnaire "as is", preservatives listed by the manufacturer, and in all patients: Colircusi tropicamida[®] (tropicamide 10 mg/ml, benzalkonium chloride, disodium edetate, chlorhydric acid, sodium chloride), Colircusi fenilefrina[®] (phenylephrine, 10%, thimerosal, disodium phosphate, sodium bisulfite), phenylephrine 1% pet., thimerosal (0.1% pet), benzalkonium chloride (0.1% aq.), and paraben mix (15%), the last 4 supplied by Marti-Tor.

If patch tests were positive, the patient was considered to be allergic to that substance. As the diagnosis of contact sensitization (Type IV) is based on the patch test, once an irritant effect was excluded, and if the patient had already had a suspicious allergic reaction to the substance, it was assumed that the subject was allergic. If patch tests were negative, conjunctival challenge was carried out.

Conjunctival challenge

Informed consent was obtained from patients. This test was carried out with the eyedrops indicated by the questionnaire if they were known, and with phenylephrine and tropicamide if they were unknown. We instilled into the conjunctival sac drops of serial dilutions. We started from 1/1000 of the original eyedrop and then increased ($\times 10$) until the eyedrop was given without any dilution. As a negative control, physiologic saline was instilled into the other eye. Readings were immediate (after 1 h) and late (1 and 2 days) at each concentration. If the highest concentration was tolerated, the patient was considered not to be allergic. A test was rated as positive if, after the challenge,

conjunctival pruritus, lacrimation, erythema or eyelid oedema appeared. In this case immediate treatment was administered.

Statistics

Familiar statistics were used for data analysis: % and their 95% confidence intervals or mean and standard deviation. To evaluate the statistical significance of the differences between proportions, a 2-tailed χ was used and Yates correction was utilized if this was necessary. For the comparison of means, the Student *t*-test was applied. The level of α significance was 5%. For data processing, the Dbase IIIp program was used and analysis was made with the Epi Info 6.0 program (1).

Results

2 patients were excluded from the study due to their refusal of conjunctival challenge. The following results refer to the other 35 patients. Sex distribution was 14 males (40%) and 21 females (60%). The mean age was 67.8 ± 6.9 years. No statistical difference was found between the patients who showed allergy and those who did not. The reason for assessment was diabetes mellitus in 7 patients, high blood pressure in 9, cataract in 6, others (retinal detachment, vitreous detachment, ocular hemorrhage, conjunctivitis, glaucoma) in 7, and unknown in 6.

There were several exposures to mydriatic eyedrops (more than 3) in 27 patients (77%). 8 patients (22.8%) had suffered more than 1 reaction before being sent to our department for investigation. The mean was 2 and the range from 1 to 4. This had no influence on the patch test result in these patients. No statistically significant difference was found (even though 25% of them were negative).

The symptoms were very similar in all patients. They complained of pruritus, lacrimation, oedematous erythema, sometimes with blepharitis, that lasted for several days (7–30). The latency of outbreak ranged from a few minutes to 24 h, with an average of 7.48 ± 6.48 h. Among the patients with allergy diagnosed by the end of the study the average interval was 8.4 ± 6.4 h, and for those not allergic it was 3.5 ± 5.6 . No statistically significant difference was found. The frequency of blepharitis as well as conjunctivitis among patients allergic to phenylephrine was 72% (21/29), and among those not allergic to it 50% (3/6). No statistically significant difference was found between each group.

The eyedrops involved were tropicamide and phenylephrine in 31 patients (83.7%), benoxinate

being associated with them in 3, fluorescein in 2, homatropine in 1 and they being unknown in 5 patients.

Patch tests

Eyedrops used "as is" were not considered to cause irritant reactions because readings at D2 were either negative or weaker than at D4 in 100% of cases. Moreover, results in the 10 healthy controls that were tested were negative. Reading at D2, allergy to phenylephrine was detected in 4 patients at the concentration of 1% and in 6 at that of 10% (Table 1). Reading at D4 was more useful, showing positive results in 14 patients at the lowest concentration and in 21 at the highest. There was a statistically significant difference between the positivity proportions of readings at D2 and D4 for 1% ($p<0.01$) as well as 10% ($p<0.001$). In 2 patients, patch testing with phenylephrine was positive after 7 and 8 days, respectively. 1 of them was challenged with the eyedrops before the patch test became positive. Consequently we can infer that, testing with only the lowest concentration of phenyleph-

rine, we would have failed to diagnose 7 patients (31.8%) who were finally considered to be allergic on patch testing. There was a statistically significant difference ($p<0.01$).

Only 1 patient had a positive patch test to thimerosal (D2 ++/D4 +++), and was negative to the other tests. Another patient who experienced a reaction after administration of benoxiprocaine, along with tropicamide and phenylephrine, had a positive (++) patch test to PPD black rubber mix at D4, and he tolerated conjunctival challenge with tropicamide and phenylephrine.

Patch tests showed allergy to phenylephrine in 62.85% of the 35 patients, to preservatives in 2.8%, and to an eyedrop other than phenylephrine in 2.8%. This diagnostic method detected the 68.57% of the patients evaluated with suspicion of contact allergy due to eyedrops.

Conjunctival challenge test

This was performed with the eyedrops involved, if the patch test was negative to both the active principles and the preservatives. Only 1 patient who

Table 1. Characteristics, skin test and conjunctival challenge results of patients allergic to phenylephrine

Patient	Sex	Age (years)	Phenylephrine 1% pet.		Phenylephrine 10% aq.		Thimerosal	Conjunctival challenge	Positive patch test D>4
			D2	D4	D2	D4			
1	M	62	—	—	—	—	—	positive (ND)	
2	M	74	—	—	—	++	—	NT	
3	F	59	—	+	—	++	—	NT	
4	M	69	—	+	—	++	—	NT	
5	M	72	—	+	—	++	—	NT	
6	F	67	—	+	—	+	—	NT	
7	F	73	—	—	—	—	—	positive (1/100)	+ phenylephrine at D7
8	F	75	—	—	—	+	—	NT	
9	F	74	+	+	+	+	—	NT	
10	M	63	—	—	+	++	—	NT	
11	F	73	+	++	+	++	—	NT	
12	F	69	—	—	—	—	—	positive (1/10)	
13	F	74	—	—	—	—	—	positive (ND)	
14	F	67	—	—	—	—	—	positive (ND)	
15	M	71	—	++	+	+++	—	NT	
16	M	64	—	—	—	—	—	positive (1/100)	
17	F	62	—	—	—	+	—	NT	
18	M	62	—	++	—	+++	—	NT	
19	F	65	—	—	—	+++	—	NT	
20	F	62	—	—	—	—	—	positive (ND)	
21	M	80	—	+	—	++	—	NT	
22	F	68	—	—	—	+	—	NT	
23	M	70	—	+	—	+	—	NT	
24	F	57	NT	NT	—	++	—	NT	
25	F	71	—	+	—	++	—	NT	
26	M	63	++	+++	++	+++	—	NT	
27	F	62	+	+++	+++	+++	—	NT	
28	M	72	—	+	—	++	—	NT	
29	F	64	—	—	—	—	—	NT	++ phenylephrine at D8

ND= not diluted. NT= not tested.

had a positive patch test at D7 was challenged with the eyedrops involved (Table 1, patient no. 7). In this case, we considered that the diagnosis was still by the challenge. The only positive tests occurred with phenylephrine application. 12 patients (34.2%) were challenged with this eyedrop. 7 of them were positive (58.3%) and the other 5 (41.6%) were negative. The latter also tolerated conjunctival challenge with tropicamide, which was the other eyedrop involved in the adverse reaction. One patient had a positive patch test to PPD black rubber mix and was not challenged with benoxiprocaine.

In summary, among the 35 patients evaluated for possible contact allergy to mydriatic eyedrops, only 1 (2.85%) reacted to preservatives (thimerosal), and another (2.85%) who was been exposed to benoxiprocaine was diagnosed as substituted-PPD-allergic and tolerated conjunctival challenge with tropicamide and phenylephrine. 29 (82.8%) patients were finally considered as allergic to phenylephrine. Among them, 75.8% (22/29) were diagnosed by patch testing, conjunctival challenge being needed to demonstrate sensitization in 7 (24.1%) (Table 2). In the remainder of the subjects, 4/35 (11.4%), all tests were negative and they were diagnosed as not allergic.

Results of the patch tests with phenylephrine are given in Tables 3 and 4. Sensitivity of the patch tests is low, even reading at D4:50% at the concentration of 1% (confidence interval 31.1, 68.9) and 72% at that of 10% (confidence interval 52.5, 86.6).

Table 2. Distribution of allergic patients by the different diagnostic methods

Patients			
Allergic 31	phenylephrine 10%	patch test D4	21
		patch test D7	1
		conjunctival challenge	7
	other eyedrops	PPD mix patch test (benoxiprocaine)	1
preservatives		thimerosal patch test	1
Not allergic 4			

Table 3. Number of patients allergic patients to phenylephrine detected by different diagnostic test

Diagnostic test	No. patients	Total
Patch test		
phenylephrine 1% D2	4 (13%)	22 (75.8%)
phenylephrine 1%	14 (48.2%)	
phenylephrine 10% D2	6 (20.6%)	
phenylephrine 10% D4	21 (72.4%)	
phenylephrine 10% D>4	1 (3.4%)	
Conjunctival challenge	7 (24.1%)	7 (24.1%)
Final diagnosis (+)		29 (100%)

Table 4. Reliability of patch tests with phenylephrine

	Phenylephrine 1% pet.		Phenylephrine 10% aq.	
	D2 (%)	D4 (%)	D2 (%)	D4 (%)
sensitivity	14.3	50	20.7	72.4
specificity	100	100	100	100
NPV	20	30	20.7	42

It was assumed that the specificity of the patch tests was 100%, once any irritant effect had been ruled out, and any patient with a positive test was considered allergic. The negative predictive value (NPV) was poor, 30% (confidence interval 12.8, 54.3) at the lowest concentration and 42% (confidence interval 18.8, 70.4) at the highest.

Discussion

In the period from January 1993 to June 1997, the 37 patients investigated due to an adverse reaction to mydriatic eyedrops constituted 5.88% of all the patch test investigations performed in our department. 35 of them finished the study. In such patients, it is the repeated administration of the kinds of eyedrops that are necessary in the assessment of various chronic conditions that appears to be the most important risk factor for sensitization to mydriatic eyedrops. The high mean age observed can be explained by the above-mentioned. 8 subjects (22.8%) had had several reactions (as many as 4) before they were referred to our department for investigation. Anamnestic data are a good indicator of allergy, 88.65% of the subjects studied being diagnosed as allergic to some substance. But if the diagnosis is assumed by this method, false-positives will be included.

The substance most frequently causing allergy in this study was phenylephrine (93.5%). When the eyedrops involved were unknown, in 100% of the cases allergy to phenylephrine was found. Tropicamide, which is used simultaneously with it, appears very safe, because none of our patients displayed allergic patch test or positive conjunctival challenge to it. Preservatives were involved in only 1 case.

In our study, the concentration most suitable to test phenylephrine at was 10% aq. (eyedrop "as is", testing preservative at the same time). Using the concentration 1%, 36.3% of the cases that could be diagnosed by patch testing were missed. Reading at D4 is most useful (68% of patients negative at D2 were positive at D4). Since 2 patients (6.89% of those allergic to phenylephrine) had patch tests only positive at D7 and D8, respectively, it may be of value to read also at this time, and to postpone conjunctival challenge until this time.

Because of the low sensitivity of the patch tests used in this study and their poor NPV we propose the necessity of conjunctival challenge. This diagnostic method is safe and has many advantages. It permitted us to identify the cause of sensitization in some patients who, due to their underlying disease, had to be exposed periodically to mydriatic eyedrops, and even to eye surgery in which these drugs are used at higher dosages. Some single case reports have been found related to reactions due to eyedrops containing phenylephrine. In these, the concentrations and vehicles used for patch testing are diverse (2–5). In no case was conjunctival challenge performed.

Eyedrops are the main source of exposure to phenylephrine, but it is also present in eardrops (6), and rectal (7) and phlebological (8) ointments, which have also caused contact dermatitis. Patients are capable of sensitization at any age: the case was reported of a neonate exposed to mydriatics who developed allergic contact conjunctivitis (9). 2 long-lasting reactions for some months after patch testing with phenylephrine have been reported (9). None of the patients in the present study showed this type of response.

As far as we know, the only prospective study of reactions to various eyedrops (mydriatics, antibiotics) in hospitalized patients was published in 1986 (11). The incidence of sensitization to phenylephrine was 2.6% among the 1526 patients studied. Nevertheless, it must be emphasised that, although patch tests were carried out, only readings at D2 were made. These were positive in 9/12 (4 of them due to phenylephrine). In their conclusions, the negative results of patch testing were interpreted as a lack of allergy and the adverse reaction then attributed to an irritant effect or to different responses on the skin of the back and the eyelids. Conjunctival challenge was not performed and it was not mentioned if the patients were later exposed to phenylephrine and if they then tolerated it or not. According to the results of our study, reading at D4 was the most reliable and even this had false-negatives at the concentrations and vehicles used. In the above-mentioned report, there were patients allergic neither to tropicamide nor to preservatives. Similar results were obtained in our study.

Another study (12) assessed 3 patterns of conjunctivitis due to long-lasting use of ophthalmic decongestants (mean 3.5 ± 4.5 years). Such patterns were related to different mechanisms: pharmacological (conjunctival hyperemia) in 71% of cases, toxic (follicular conjunctivitis) in 24%, and allergic (blepharoconjunctivitis) in 4%. Patch tests were not performed.

Conclusions

A clinical questionnaire is a good indicator of contact allergy to mydriatic eyedrops.

The probability of this being sensitization to phenylephrine is very high in Spain.

Patch testing must include reading at D4 and even at D7.

Patch testing with 10% aq. is highly specific but it has low sensitivity. In the presence of a negative patch test, the possibility of allergy cannot be excluded because its negative predictive value is low.

These observations lead us to suggest that conjunctival challenge appears to be a safe and accurate method to identify eyedrop allergy.

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