

Contact allergy to beryllium chloride: report of 12 cases

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Summary

Background. Isolated cases of allergic contact dermatitis, gingivitis and stomatitis caused by beryllium have been previously reported. We have been able to study a series of 12 patients with patch test reactions to beryllium chloride.

Objectives. The study was aimed at defining the clinical and patch testing characteristics in this group of patients, and determining whether some were delayed elicitation reactions or late reactions of active sensitizations by patch testing.

Material and methods. We performed a 5-year retrospective study of patients tested with a metal series, and studied a subgroup who showed reactions to beryllium chloride.

Results. A total of 1799 patients were patch tested, 62 of whom were also tested with a specific metal series; 12 of them reacted to beryllium chloride. Eight of the 12 patients showed reactions to other metals. Based on the time of positive reaction to beryllium chloride, three patterns emerged: (i) 3 patients showed positive reactions on D2–D4; (ii) 6 patients showed positive reactions between D7 and D10; and (iii) 3 patients showed positive reactions later than D10.

Conclusions. Contact allergy to beryllium chloride may not be as unusual as the literature suggests. In order to avoid undetected contact allergies, we recommend performing later readings, between D7 and D10, whenever patch testing is performed with beryllium chloride. Active sensitization may occur.

Key words: active sensitization; beryllium chloride; delayed reactions; late reactions; patch test.

Beryllium is a low molecular weight metal, with a high fusion temperature and high permeability to X-rays, and is an excellent thermal and electric conductor. It is used in alloys with copper, nickel, or aluminium (1, 2). It has multiple applications, including in electrical and ceramic materials, fluorescent tubes, and the aeronautical and aerospace fields (1–3). An important use has been in alloys with nickel, chromium, cobalt, molybdenum and, sometimes, aluminium for dental prostheses (1, 4, 5). However, concerns about carcinogenicity (beryllium has

been classified by the International Agency for Research on Cancer (6) and the EU (7) as a human carcinogen) led to its replacement by yttrium, to which no adverse reactions have yet been observed (8), although beryllium is still used in some dental prostheses.

Beryllium exposure can cause acute or chronic effects in the skin or pulmonary system. Pulmonary berylliosis, through inhalation of beryllium particles, has been described (4). When beryllium particles are inhaled in high concentrations, acute chemical pneumonitis can develop; however, prolonged exposure to beryllium is required for the development of non-caseating granulomas.

Five groups of cutaneous disease have been described: irritant contact dermatitis, allergic contact dermatitis, chemical ulcers, ulcerating granulomas, and allergic dermal granulomas (9). Acute exposure can result in papules,

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vesicles, and pustules. Chronic exposure can result in a granulomatous reaction (3). Insoluble forms (beryllium oxide) can cause granulomas (3, 4), whereas soluble salts (fluoride, sulfate, and chloride) are readily hydrolysed and can produce contact sensitization. Beryllium is able to bind to tissue proteins and produce a complete antigen (7). Early studies confirmed that it is a contact sensitizer according to the test of Magnusson and Kligman (10). Beryllium fluoride is a potent sensitizer, and has caused allergic contact dermatitis in persons who have handled it. As beryllium sulfate and beryllium chloride have lower sensitization capacity, they have been recommended for use in patch tests (3, 11).

Although beryllium has been classified as a skin sensitizer (7, 10), base metal alloys containing it remain in widespread use (5, 12, 13).

Although there have been reports of isolated cases of allergic gingivitis and stomatitis caused by contact with beryllium in wearers of dental prostheses (8, 12–14), as well as allergic contact dermatitis on the hands of dental technicians (12), it was thought unlikely that cutaneous contact with metallic beryllium or its alloys could generate a sufficient quantity of soluble compound to induce allergy (1).

Our group recently reported 2 cases of contact allergy to beryllium chloride (15). Since that time, we have been able to study a further 10 cases. The present study was aimed at defining the clinical and patch test characteristics in this total group of 12 patients, and determining whether some of the patch test reactions were delayed elicitations or late active sensitizations.

Material and Methods

We performed a retrospective and descriptive study at a tertiary referral hospital. We reviewed all patients who, between January 2004 and May 2010, had undergone patch testing with a metal series (Martí-Tor®), and studied a subgroup who had positive reactions to beryllium chloride. All of the patients were tested with the baseline of the Spanish Group for Research into Contact and Skin Allergy (GEIDAC) and/or the Martí-Tor® metal series and any other tests considered to be relevant in each case. Patch testing with the metal series was undertaken in those patients who showed positive reactions to one or more metals detected by the GEIDAC baseline series and who were due to receive a metal prosthesis (dental or orthopaedic). We also tested with the metal series when there was a high level of suspicion of an occupational or non-occupational allergic contact dermatitis caused by metals but no positive result was obtained with the GEIDAC baseline series. The allergens used in the GEIDAC

baseline series were supplied by Chemotechnique® Diagnostics AB. This baseline series includes the following: nickel sulfate, 5%; cobalt chloride, 1%; potassium dichromate, 0.5%; and mercury metal, 0.5%. The Martí-Tor® series consists of 33 metals, including beryllium chloride 1% in petrolatum (pet.). The patches were prepared with Finn Chambers® on Scanpor® tape, and were removed after 2 days. Readings were taken at D2 and D4, with the evaluation criteria (+, ++ and +++) recommended by the International Contact Dermatitis Research Group. In those cases with a doubtful result at D4, a further reading was made at D7.

'Late reactions' were defined as a reaction noticed (by the patient or someone else) at least 10 days after the application of the test, and which was negative on the D4 reading (16). We registered as a reading the day on which a patient returned to see us because they had noticed a late-onset positive reaction at the patch test site. These patients underwent repeat testing with the suspected metals.

We studied the relevance of each positive reaction. The relevance was considered to be: (i) current if the symptoms could be wholly or partially attributed to beryllium contact allergy; (ii) past if it explained a previous symptom; and (iii) unknown if the symptoms could not be attributed to beryllium contact allergy.

The information was obtained from our computerized database. The clinical data recorded on each patient were age, sex, profession, site of lesions, series tested, positive reactions, number of positive reactions, relevance of positive reactions, origin of the sensitization, and diagnosis. We also recorded the time of onset of positivity to beryllium chloride.

Results

From January 2004 to May 2010, a total of 1799 patients underwent patch testing, all with the GEIDAC baseline series. Of these patients, 62 (3.45%) were also tested with a metal series, with 12 of them (19.3%) testing positive with beryllium chloride. Table 1 shows the clinical and demographic characteristics of these 12 patients. The metal salts for which positive patch test reactions were recorded in these 62 patients were nickel sulfate in 24 (38.7%), cobalt chloride in 12 (19.3%), beryllium chloride in 12 (19.3%), potassium dichromate in 8 (12.9%), and palladium chloride in 8 (12.9%).

A positive reaction to beryllium chloride at the D4 reading was found in only 3 of the 12 positive patients. It occurred between D7 and D10 in 6, and between D10 and D20 in the remaining 3 (Fig. 1). We retested 6 of the 9 patients who were positive on D7 or later, because of

Table 1. Clinical characteristics and patch test results in patients reacting to beryllium chloride 1% pet

Patient no.	Sex	Age (years)	Profession	History of atopy	Localization	Diagnosis	Number of positive reactions	Allergens	Day on which a positive reaction to beryllium was seen (first test)	Comment
1	♀	51	Healthcare worker	—	Upper eyelid	ACD	7	Ni, Pd, Au, Thio, MDBGN, Qui, and Be	7	Concomitant patch test reactivity
2	♀	66	Housewife	No	Oral mucosa	ACD	1	Be	4	Dental prosthesis. Improved after removal of dental prosthesis
3	♀	10	Student	PA	Diffuse (including periumbilical)	ACD	4	Ni, Pd, Au, and Be	10	Concomitant patch test reactivity
4	♀	19	Student	No	Diffuse	ACD	3	Ni, Pd, and Be	2	Concomitant patch test reactivity
5	♀	54	Clerk	No	Interdigital	ICD	3	Ni, Co, and Be	10	Concomitant patch test reactivity
6	♀	42	Other	No	Trunk	ACD	2	Ni and Be	15	Concomitant patch test reactivity versus active sensitization
7	♂	22	Metal industry worker	PA	Fingertips	ACD	1	Be	7	Professional. Improved after avoidance of beryllium metal moulds
8	♀	14	Student	FA	Lips	ACD	1	Be	15	Dental braces. Improved after removal of braces
9	♀	28	Clerk	No	Diffuse (including periumbilical and ear lobes)	ACD	4	Ni, Co, Pd, and Be	7	Concomitant patch test reactivity
10	♂	25	Sculptor	—	Generalized (starting on feet)	ACD	3	Carba, Sn, and Be	20	Probable active sensitization
11	♀	47	Housewife	PA and FA	Oral mucosa	ACD	4	Ni, Co, Cr, and Be	4	Dental prosthesis. Awaiting prosthesis withdrawal
12	♀	29	Education	AD	Ears	Infection	1	Be	10	Probable active sensitization. Positive on D2 after retesting

♀, female; ♂, male; PA, personal atopy; FA, family atopy; AD, atopic dermatitis; ACD, allergic contact dermatitis; ICD, irritant contact dermatitis; Diffuse, affecting three or more sites; Ni, nickel sulfate 5% pet.; Pd, palladium chloride 1% pet.; Be, beryllium chloride 1% pet.; Co, cobalt chloride 1% pet.; Au, gold sodium thiosulfate 0.25% pet.; Thio, thimerosal 0.1% pet.; MDBGN, methyldibromo glutaronitrile 0.1% pet.; Qui, quinoline mix 6% pet.; Carba, carba mix 3% pet.; Cr, potassium dichromate 0.5% pet.; Sn, tin chloride 0.5% pet.

difficulty in correctly identifying the allergen responsible for the reaction. All 6 had a positive reaction to beryllium chloride between D2 and D4 (Fig. 1).

Of the 12 patients who showed positive reactions to beryllium chloride, 8 also showed positive reactions to other metals. In 6 of these 8, positivity appeared on D7 or later. Among 4 of the 12 patients with monosensitization to beryllium chloride, 1 showed a positive reaction before

D7, and in the other 3, positive reactions to beryllium chloride did not appear until D7 or later.

Contact allergy to beryllium chloride in our series of patients was considered to be of occupational origin only in patient 7, who worked with metal moulds for plastic pieces engraved with copper and beryllium. After avoidance of contact with these moulds, the patient's symptoms resolved. In 8 patients, the source of exposure to beryllium

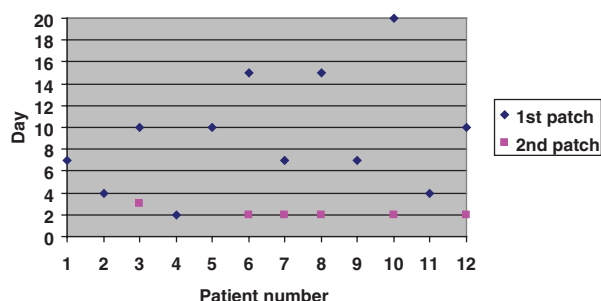


Fig. 1. Day of positive reaction to beryllium chloride 1% pet. Blue spots represent the first patch test, and pink spots represent the second patch test.

was considered to be related to metals (dental prosthesis in patients 2 and 11, dental braces in patient 8, and concomitant patch test reactivity to other metals in patients 1, 3, 4, 5, and 9). In the other 3 patients, the origin of the exposure was unknown (patients 6, 10, and 12) (Table 1).

Discussion

To date, only a few isolated cases of allergic contact dermatitis caused by beryllium chloride have been reported (8, 12–15) (Table 2). This suggests that this entity is unusual, but since the inclusion of this metal salt in a specific series, we have shown that contact allergy to beryllium chloride is not rare; indeed, in our group of patients tested with a metal series, we detected more positive responses to beryllium chloride than to other metal salts included in the baseline series, such as potassium dichromate. We are aware that we have a small and selected sample, but our results agree with those of Vilaplana et al. (11), and they suggest that beryllium chloride should be included in all metal series. Consequently, it would be interesting to determine the true frequency of contact allergy to beryllium chloride in populations undergoing routine patch testing.

In the previously reported cases of delayed hypersensitivity to beryllium chloride, beryllium was the only metal to which the affected patients tested positive (12, 13). This, however, was only true in one-third of our patients. The remaining two-thirds were sensitive to various other metals as well. This is not unusual among patients who are allergic to a metal, and it could be interpreted as concomitant contact allergy or as cross-reactions.

On the basis of the time of detection of positive patch test reactions to beryllium chloride in our series, three clinical situations can be determined:

- (1) Patients in whom a positive reaction to beryllium chloride was detected on the usual days

for readings (D2–D4). This situation was seen in 3 patients (patients 2, 4, and 11). Two of them had lichen planus-like oral mucosal involvement (patients 2 and 11), involving the areas close to a metal prosthesis (patient 11) or with disappearance of the lesions after removal of the prosthesis (patient 2); unfortunately we were not able to analyse the prostheses. These patients were similar to most of the patients previously described (8, 12–14), and their condition may have been an allergic contact stomatitis. Patient 4 had a diffuse eczema on the areas of contact with metal objects (e.g. ear lobes), which was probably attributable to concomitant allergic contact dermatitis caused by other metals, such as nickel.

- (2) Patients in whom a positive reaction to beryllium chloride was seen between D7 and D10. This situation was seen in 6 of the 12 (50%) positive patients. In 4 of these (including the 2 patients with a positive reaction on D10), positive reactions to other metals were detected, which we interpreted as concomitant patch test reactivity. We consider that these 6 cases were delayed elicitation reactions to beryllium chloride. Accordingly, we recommend readings on D7 and D10 with patch tests for metals that include beryllium chloride, as otherwise many patients might not be detected. Patient 7, who worked with metal moulds for plastic pieces engraved with copper and beryllium, had allergic contact dermatitis caused by beryllium chloride as a result of his occupation, a situation that has only been reported once (12), although cases of professional sensitization to beryllium fluoride have been reported (11).
- (3) Patients in whom a positive reaction to beryllium chloride was detected later than D10, probably representing active sensitization by patch testing. Active sensitization occurred in 3 patients in our series (patients 6, 8, and 10). These 3 patients were retested with beryllium chloride, and positive reactions occurred before D4, which conforms to the classic definition of active sensitization, defined as the development of a reaction at the test site after D10–D20 and an early positive reaction (D2–4) on retesting with the allergen in question (16–19). However, the symptoms of patient 6, who only showed contact allergy to beryllium chloride, remitted after removal of their dental braces, and therefore we cannot rule out a delayed elicitation reaction.

Table 2. Patients reported in the literature with contact allergy to beryllium salts

Authors	Number of patients	Localization of the lesions	Positive reaction to beryllium	Patch test results	Comments
Curtis (11)	Thirteen patients (workers at beryllium-extraction plants)	Predominantly exposed areas: face, neck, arms, and chest	Thirteen patients with BeF ₂ , 10 patients with BeSO ₄ , 8 patients with BeCl ₂ and 8 patients with Be(NO ₃) ₂ . Positive reading at 72 hr	Not performed	8/16 controls sensitized to inorganic beryllium salts
Vilaplana et al. (12)	Three patients	Case 1: Lesions on oral mucosa in contact with dental prosthesis	Metal series: Positive at D2 and D4 to BeCl ₂ 1% pet.	Standard series (TRUE® test) and dental series (Chemotechnique): Negative	Monosensitization
		Case 2: Pulpitis in manufacturer of dental prostheses	Positive at D2 and D4 to BeCl ₂ 1% pet.	Negative	Monosensitization
		Case 3: Eczematous lesions over humeral interosseous prosthesis	Positive at D2 and D4 to BeCl ₂ 1% pet.	Negative	Monosensitization
Haberman et al. (13)	Two patients	Case 1: Lesions on oral mucosa in contact with dental prosthesis	Beryllium sulfate 1%: Positive at D7	Standard series (NACDG), metal tray (OHSU) and dental acrylates: negative	Monosensitization
		Case 2: Gingivitis in area near a dental bridge	Beryllium sulfate 1%: Positive at D4	Standard series (European), metal and dentistry series: negative	Monosensitization
Lucas et al. (15)	Two patients	Case 1: Eczematous areas where she wore jewellery	Metal series: Positive at D15 to BeCl ₂ 1% pet. Positive at D3 in the second patch test	Standard series (GEIDAC) and metal series (Marti-Tor): nickel sulfate, palladium chloride and gold sodium thiosulfate positive	Cosensitization
		Case 2: Generalized eczema starting on feet	Metal series: Positive at D20 to BeCl ₂ 1% pet. Positive at D2 in the second patch test	Standard series (GEIDAC), metal and rubber series (Marti-Tor): carba mix-positive and tin chloride-positive	Possible active sensitization

BeF₂, beryllium fluoride; BeSO₄, beryllium sulfate; BeCl₂, beryllium chloride; Be(NO₃)₂, beryllium nitrate; NACDG, North American Contact Dermatitis Group; OHSU, Oregon Health and Science University; GEIDAC, Grupo Español Investigación Dermatitis Alérgica de Contacto (Spanish Contact Dermatitis Research Group).

An earlier reaction after retesting an allergen can also be interpreted as a booster effect (16, 17), as occurs in other immunological reactions, for example with the Mantoux test. It is difficult to demonstrate that active sensitization has occurred by patch testing; to reduce the possibility of it occurring, a possible recommendation would be to reduce the concentration of beryllium chloride in the test series. Active sensitization by a beryllium salt was mentioned by Curtis in 1951 (11), who reported that 8 of 16 controls had been sensitized to beryllium fluoride, and proposed performing patch testing with beryllium chloride or beryllium sulfate.

Haberman et al. (13) patch tested 30 controls with beryllium sulfate 1%, and no reactions, irritant or allergic, were observed.

Conclusions

As is the case with other allergens that are not often used for testing, the true incidence of contact allergy to beryllium chloride is unknown, but our experience suggests that it is not as unusual as the literature suggests (1). Accordingly, we recommend patch testing with beryllium chloride for patients sensitized to metals in whom a metal

prosthesis (and particularly a dental prosthesis) is due to be placed or has been placed, and in patients with eczema with exposure (occupational or non-occupational) to beryllium.

Active sensitization by patch testing with beryllium chloride 1% pet. seems to occur, and it may be necessary to reduce the concentration of beryllium chloride in the test series.

In most cases with a positive reaction to beryllium chloride, we found concomitant patch test reactivity to multiple other metal salts, although up to one-third of patients were sensitized to beryllium chloride alone.

In order to avoid undetected contact allergies to beryllium, we recommend performing later readings, preferably between D7 and D10, whenever patch testing is performed with beryllium chloride.

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