

Occupational Rhinitis and Asthma Due to EDTA-Containing Detergents or Disinfectants

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Background Detergents and disinfectants are an emerging cause of work-related rhinitis and asthma. These products may contain ethylenediamine tetraacetic acid (EDTA). The authors report 10 cases of EDTA-related asthma and/or rhinitis.

Methods Review of the medical charts of patients who presented with work-related rhinitis (alone or with asthma), with a history of exposure to aerosols of EDTA-containing products and who underwent a nasal provocation test (NPT) with tetrasodium EDTA (1–4%) in our occupational health unit.

Results Twenty-eight patients underwent a NPT with EDTA, which was positive in 10 cases. These patients, mostly cleaners or healthcare workers, used spray formulations of cleaning products.

Conclusions This case series is the first report of EDTA-related respiratory disease, documented by a specific test. An irritant mechanism is unlikely. Further studies are required to distinguish between an immunoallergic response and a pharmacological mechanism possibly resulting from calcium chelation, as suggested by animal experiments. A ban of spray preparations would be sufficient to prevent respiratory disease induced by EDTA inhalation, regardless of its mechanism. *Am. J. Ind. Med.*

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KEY WORDS: rhinitis; asthma; occupational disease; ethylenediamine tetraacetic acid; nasal provocation test

INTRODUCTION

Cleaners are a group of workers at risk of developing occupational rhinitis and/or asthma [Zock et al., 2010]. Among the cases of occupational asthma (excluding work-exacerbated asthma) identified by the “Observatoire National des Asthmes Professionnels” (ONAP, French national observatory of occupational asthma) during the

1996–1999 period [Ameille et al., 2003], cleaning agents were the seventh most common cause, accounting for 3.6% of cases. Nine years later, cleaning agents had become the second most common cause, accounting for 12.2% of cases identified by the ONAP in 2008 [Ameille and Hamelin, 2010]. A similar pattern has been observed for occupational rhinitis, as cleaners represented 2.7% of all cases diagnosed in the four occupational health units of the Paris region in 1997–1998 and 8% of cases between 1999 and 2003 [Garnier et al., 2010]. The risk of developing rhinitis and/or asthma is also increasing in healthcare professionals who also use detergents and disinfectants [Arif et al., 2009].

These epidemiological data can most likely be explained by the growing use of aerosolized cleaning products, as aerosols increase respiratory tract exposure to the irritant and/or sensitizing agents contained in these products. Quaternary ammoniums are both irritant and sensitizing substances. As these substances are

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components of many cleaning agents and disinfectants, they are often considered as responsible for respiratory symptoms observed in cleaners and healthcare professionals [Ameille and Hamelin, 2010]. However, disinfectants and cleaning products may contain many other irritant or sensitizing agents that may also be involved in respiratory reactions.

We report the first series of cases of rhinitis with or without asthma in workers exposed to aerosolized cleaning agents or disinfectants, in whom ethylenediamine tetraacetic acid (EDTA) sodium salts were the most likely cause of respiratory symptoms, as demonstrated by nasal provocation tests (NPTs). After describing the features of NPT positive and NPT negative cases, possible mechanisms for the effect of EDTA on the respiratory tract are considered.

MATERIALS AND METHODS

Patients

All patients investigated by a NPT with EDTA for the diagnosis of occupational rhinitis (alone or associated with asthma) in our occupational health unit between January 2002 and July 2010 were identified. Their medical records were analyzed to determine whether their NPT was positive or negative.

NPT Test Procedure

There is no consensus at the present time concerning the NPT test procedure [Litvyakova and Baraniuk, 2001]. However, review of our cases showed that all tests were performed according to the same protocol by a single operator. The response of the nasal mucosa was measured by posterior rhinomanometry. This technique consists of simultaneous recording the pressure difference between the nostril and posterior nasal aperture, and nasal airflow during the respiratory cycle, from which the total nasal resistance (NR) is calculated. NPT was performed after stopping antihistamine, corticosteroid, or vasoconstrictor treatment for at least 1 week. A pretest measurement of NR detected the presence of any baseline nasal obstruction, in which case the NPT was postponed. The NR measurement 15 min after spraying normal saline into each nostril was used as the baseline value. EDTA was then sprayed into each nostril (0.1 ml of an aqueous solution of EDTA) immediately after maximum inspiration to prevent the solution from entering the lower airways. A nose clamp was immediately attached and maintained for 15 min before the subject was allowed to blow his/her nose. NR was measured 15 min after the end of the challenge. The criterion for a positive NPT was doubling of the baseline value. The clinical signs observed during the

NPT were also recorded. Any delayed signs were investigated at a clinical examination performed several days later.

Substances Tested by NPT

The complete composition of each product used by each patient in the workplace was obtained from the manufacturer. NPT were performed with all potentially sensitizing substances present in the formulation of one or more products. EDTA tests were always performed with aqueous solutions of the tetrasodium salt (EDTANa_4). No consensus has been reached concerning the EDTA concentration used for NPT. Two of the early cases were investigated with a 4% solution, and a 1% or 2% solution was systematically used thereafter (as generally proposed for patch testing). Only one concentration was used for each patient.

Other Data

The following items were also investigated: patient's occupation, EDTA concentration in the products used, dispersion method (sprayed or not) of the commercial product, presence of rhinitis symptoms (itchy nose, sneezing, rhinorrhoea, nasal obstruction), presence of asthma-like symptoms (cough, dyspnea, wheeze, chest tightness), and atopy (defined as past history of allergic respiratory illness or presence of at least two of the following laboratory criteria: serum total IgE greater than 100 IU/L, at least two positive prick tests to common respiratory allergens, positive Phadiatop test).

Pulmonary function tests were performed in all patients and the presence of a global obstructive syndrome, a distal obstructive syndrome, and/or non-specific bronchial hyperreactivity (NSBHR) was recorded. Global obstructive syndrome, distal obstructive syndrome and NSBHR were respectively defined as: (1) forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) < 70%; (2) midrespiratory flow between 25% and 75% of FVC (MEF_{25-75}) < 70%; and (3) a decrease in FEV_1 of at least 20% for a cumulative dose of methacholine of 1,600 μg or less.

RESULTS

Twenty-eight patients underwent an EDTA test. Patient characteristics are reported in Table I. They were mostly cleaners or healthcare professionals, except for one of the patients with a positive EDTA-NPT (who was a supermarket employee) and four patients with a negative EDTA-NPT (who worked in medical device maintenance, disinfectant packaging, wood frame treatment, and welding, respectively). The occupational origin of the

TABLE I. Patient Characteristics

	Positive EDTA-NPT	Negative EDTA-NPT
Patients	10	18
Gender, female	7	14
Age, median [range] (years)	46.0 [38–63]	42.5 [22–57]
Symptoms		
Rhinitis alone	2	11
Rhinitis and asthma-like syndrome	8	9
Atopy	5	6 ^a
Occupation		
Cleaners	5	8
Healthcare professionals	4	6
Others	1	4
EDTA % in products, median [range]	2.5 [0.02–12]	2.5 [0.08–25]
EDTA concentrations used in the NPT		
1%	6	10
2%	3	7
4%	1	1
Patients reacting/tested with one or more other product(s)	3/9	6/16

^aMissing data for two patients.

respiratory symptoms was suspected in every case on the basis of their chronology (recurrence of symptoms after exposure to the suspected products in the workplace and resolution of symptoms after cessation of exposure).

Patients With a Positive EDTA-NPT

All EDTA-containing products were detergents or disinfectants, except in one patient, who used an EDTA-containing air freshener. The EDTA compounds concerned were always the disodium and/or tetrasodium salts, and most patients were exposed to the disodium salt alone or together with tetrasodium EDTA. Four workers used more than one EDTA-containing product. All patients used their EDTA-containing product(s) in spray-formulations. Four patients had a history of allergy (two had urticaria to latex and the other two had seasonal rhinitis related to pollen allergy). Two other patients had a history of asthma: one case of occupational irritant-induced asthma and another case of childhood asthma. Pulmonary function tests were performed in all patients and showed a global obstructive syndrome in two cases, a distal obstructive syndrome in two other cases and only moderate NSBHR (PD₂₀: 800 µg of methacholine) in the fifth patient. An NPT with at least one other substance (quaternary ammoniums, amines, aldehydes, or sulphites) was performed in 9 of the 10 patients. One patient had positive tests for two other

substances: didecyltrimethylammonium chloride (0.2% in water) and *N*-lauryl-*N,N*-dimethylamine oxide (0.5% in water). Two patients had a positive test for one other substance: alkyltrimethylbenzylammonium chloride (0.1% in water) and didecyltrimethylammonium chloride (0.2% in water), respectively.

Patients With a Negative EDTA-NPT

These patients were more likely to have rhinitis alone than those with a positive EDTA challenge. Pulmonary function tests showed a global obstructive syndrome in two patients, a distal obstructive syndrome in seven patients (associated with NSBHR in six patients), and one case of isolated NSBHR. NPT with at least one other substance was performed in 16 patients and these tests were positive in six cases: didecyltrimethylammonium chloride in two cases and alkyltrimethylbenzylammonium chloride, *N*-lauryl-*N,N*-dimethylamine, aminopropyl laurylamine, and a mixture of several amines and quaternary ammoniums, in one case each.

DISCUSSION

We report 10 cases of work-related asthma and/or rhinitis associated with a positive NPT with 1–4% tetrasodium EDTA aqueous solutions. The incidence of EDTA-induced occupational rhinitis and asthma is probably severely underestimated. EDTA is often associated in commercial products with other substances known to be potential respiratory allergens (for instance, quaternary ammoniums, amines, aldehydes, etc.). On the basis of their notoriety, these substances are frequently considered to be responsible for the work-related symptoms without any further investigations. When present in aerosolized products, EDTA or EDTA salts should be considered to be a possible cause of work-related rhinitis and asthma, and specific NPT should be performed to document this hypothesis.

Specific NPT are the gold standard to establish the cause of occupational allergic rhinitis [Moscato et al., 2008; Didier et al., 2010]. NPT tries to reproduce the symptoms experienced in the workplace and, when positive, constitutes a strong argument in favor of the responsibility of the allergen tested. This test is easy to perform and generally well tolerated. The gold standard for the diagnosis of occupational asthma is a specific bronchial provocation test [Kopferschmitt-Kubler et al., 2008]. However, as it may be difficult to control the intensity of bronchial exposure, the test can cause severe bronchospasm. It can therefore only be performed in a few specialized centers close to an emergency unit [Cartier et al., 1987]. This test is therefore rarely used. Occupational allergic asthma is often associated with rhinitis, and generally occurs after

rhinitis [Garnier et al., 2010]. This suggests a pathophysiological continuum between the two entities. A good correlation has been demonstrated between the response to NPT and the response to the bronchial provocation test in these people who present with both allergic asthma and rhinitis [Koh and Choi, 2002]. NPT is therefore an acceptable alternative to the bronchial test in cases of allergic occupational asthma associated with rhinitis.

The positive NPT demonstrates that rhinitis (and asthma when it is associated with rhinitis) is due to EDTA, but the mechanism of the reaction is unknown and could be irritant, pharmacological, and/or immunoallergic.

The hypothesis of an irritant mechanism responsible for the positive responses to EDTA-NPT is unlikely to be true. Firstly, experiments in dogs have shown that inhalation of a 6% calcium disodium EDTA aerosol did not induce any increase in bronchial resistance [Downes and Hirshman, 1983]. Most of the NPT in this series used 1% EDTA, as recommended for skin testing [Fisher, 1986]. The other tests with more highly concentrated solutions (2% and 4%) did not induce a larger proportion of positive results. Furthermore, skin testing with a 10% solution did not induce any reaction [Kimura and Kawada, 1999]. It has also been established that exposure to irritants can only moderately increase NR: for example, Shusterman et al. [1998, 2005] showed a 20–30% increase of NR after provocation with chlorine gas or acetic acid vapor. Doubling of NR, the criterion used for a positive NPT in this series, is suggestive of an allergic or pharmacological response rather than irritation. The negative response to EDTA-NPT in a large number of patients of this series given the same test dose also makes a non-specific irritant response an unlikely explanation for the positive tests.

Experiments in dogs indicate that the increased bronchial resistance observed after inhalation of EDTA sodium salts might also have a pharmacological mechanism. In this species, inhalation of 6% disodium EDTA aerosol caused a significant increase in bronchial resistance, while inhalation of the same concentration of calcium disodium EDTA had no effect [Downes and Hirshman, 1983; Lindeman et al., 1990]. The two aerosols had the same characteristics (pH, osmolality, concentration of EDTA) but only one induced bronchoconstriction. The only apparent difference between the two preparations is that disodium EDTA is able to bind calcium, while calcium disodium EDTA does not bind calcium. The bronchoconstriction induced by disodium EDTA thus could be due to calcium chelation. Similarly, increased non-specific bronchial reactivity to methacholine was observed in dogs first exposed to EDTA disodium salt; this effect was not observed when calcium disodium, rather than the disodium salt, was used [Lindeman et al., 1991]. No experiments have been conducted with EDTA tetrasodium salts—the EDTA salt used for the NPT performed in this series—but

like the disodium salt, it is a calcium-chelating agent. This pharmacological effect of EDTA sodium salts may induce bronchoconstriction in workers exposed to EDTA-containing preparations. It may also facilitate bronchoconstriction induced by associated sensitizing and/or irritant agents.

As EDTA is generally used as a calcium-chelating agent in cleaning and other commercial products (in order to prevent deposition of calcium from water on surfaces), EDTA compounds in commercial preparations are usually disodium and/or tetrasodium salts, as in every case in this series.

The large number of negative NPT in this series does not constitute an argument against this pharmacological hypothesis, in view of the marked interindividual variability observed in these pharmacological reactions.

Respiratory symptoms after inhalation of EDTA aerosols could also have an immunoallergic mechanism. No cases of human EDTA-related occupational rhinitis or asthma have been reported prior to the present series. However, sodium salts of EDTA have been suspected to be responsible for paradoxical bronchospastic reactions after inhalation of bronchodilating preparations containing low concentrations of EDTA salts as additives. Two studies have tested this hypothesis by performing specific bronchial provocation tests with EDTA in asthmatic patients. The two published articles did not specify whether EDTA itself or one of its salts was used. In one study, the tests were performed with a 0.02% EDTA solution and no bronchial reaction was observed [Asmus et al., 2001]. In the other study, a bronchial provocation test with EDTA was performed in six patients who had previously presented bronchospasm after inhalation of an EDTA-containing bronchodilating preparation [Beasley et al., 1987]. All patients responded positively (at least 20% decrease of FEV₁) at concentrations of 0.12–1.28% (mean 0.24%), higher than in the bronchodilating preparation. All patients also had positive bronchial provocation tests with benzalkonium chloride, the preservative used in the preparation. The positive reactions obtained with EDTA in all patients but only at concentrations higher than those of the incriminated preparation used previously by these patients constitute a strong argument in favor of a pharmacological rather than an immunoallergic mechanism. On the other hand, the tested concentrations were too low to be irritant.

True cutaneous allergic reactions to EDTA have been reported, but only a few cases of non-occupational allergic contact dermatitis to EDTA [Raymond and Gross, 1969; de Groot, 1986; Soga et al., 2003; Pruitt and Warshaw, 2010] or its disodium [Bhushan and Beck, 1998], trisodium [Kimura and Kawada, 1999], or tetrasodium [Sanchez-Pedreno et al., 2009] salts have been published. Local allergic reactions with eosinophilic infiltrates

after subcutaneous injection of apomorphine with EDTA preparations (but not with apomorphine alone) have also been reported [van Laar et al., 1998]. Given the ubiquitous nature of EDTA in cosmetics, domestic, and professional preparations, it would appear to be a weak skin sensitizer.

EDTA is an ethylenediamine derivative. Ethylenediamine, like other aliphatic amines, is a known sensitizing agent [Zuidema, 1985]. Aminophylline results from the linkage of ethylenediamine to theophylline; it has been responsible for numerous cases of allergic contact dermatitis [Baer et al., 1959] but also for cases of allergic reactions after systemic administration: eczema [Walker and Ferguson, 2004], urticaria [Urbani, 1994], exfoliative erythroderma [Elias and Levinson, 1981], and baboon syndrome [Guin et al., 1999]. Numerous cases of occupational asthma to ethylenediamine have also been reported since 1963 [Gelfand, 1963; Lam and Chan-Yeung, 1980; Aldrich et al., 1987] and some of them have been documented by specific bronchial provocation tests [Nakazawa and Matsui, 1990; Ng et al., 1991, 1995; Casas et al., 2002; Villar-Gomez et al., 2009]. Cross-reactions between EDTA and ethylenediamine in skin tests have been reported [Raymond and Gross, 1969; Eriksen, 1975], but appear to be rare [Provost and Jillson, 1967; Epstein, 1974; Fisher, 1975; Balato et al., 1986; de Groot, 1986; Bhushan and Beck, 1998; Pruitt and Warshaw, 2010].

CONCLUSION

This article reports the first 10 published cases of occupational asthma and/or rhinitis in patients exposed to EDTA-containing products. The responsibility of EDTA salts was confirmed by specific NPTs, using non-irritant concentrations of EDTA sodium salts.

The mechanism of the respiratory symptoms induced by inhalation of aerosolized EDTA sodium salts may be immunoallergic or pharmacological, as it has been experimentally demonstrated that EDTA disodium salt solutions can increase bronchial reactivity and bronchial resistance via a pharmacological mechanism (probably linked to the calcium-chelating activity of EDTA sodium salts). To further our understanding of the mechanisms involved, any future cases should be investigated by NPT successively using the disodium (or tetrasodium) salt, followed (when a positive response is obtained with a sodium salt) by the calcium disodium salt: a negative response to the second test would indicate that a pharmacological mechanism is highly probable.

At usual room temperatures, EDTA and its salts are not volatile substances [Anonymous, 2004]. In the workplace, exposure can only result from aerosol production. A ban on spray preparations would be sufficient to prevent respiratory disease induced by EDTA inhalation, regardless of its mechanism. This is also true for quaternary

ammoniums, the other main chemical agents currently responsible for occupational respiratory diseases in professional cleaners. If the use of these spray preparations cannot be banned, workers should be equipped with respiratory protection.

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