CASE REPORT

Anaphylaxis and allergic contact urticaria from occupational airborne exposure to HBTU

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Abstract

We describe a case of anaphylaxis and allergic contact urticaria from occupational airborne exposure to HBTU (o-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate), which is a chemical used widely for solid and solution-phase peptide synthesis. Previously, the use of this chemical has been associated with occupational asthma, allergic contact urticaria and allergic contact dermatitis in individual cases, but not with anaphylaxis. Our diagnoses were based on the clinical symptoms, positive skin prick test (SPT) and positive skin provocation test to HBTU. The positive SPT indicates that the anaphylaxis reaction was IgE-mediated. We recommend that in the handling of HBTU, appropriate safety measures should be compulsory, and if work-related symptoms develop, the possibility of anaphylaxis should be considered in advising on appropriate work tasks.

Key words

Allergic contact urticaria; anaphylaxis; CAS 94790-37-1; HBTU; peptide synthesis.

Introduction

The laboratory chemical HBTU (o-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate) is a coupling reagent used widely for solid and solution-phase peptide synthesis, in which it is used with 9-fluorenlymethoxycarbonyl amino acids (f-moc amino acids) [1]. HBTU is a white crystalline powder (molecular weight 379.3 g/mol, CAS 94790-37-1) (Figure 1).

Previously, one case of occupational contact urticaria [1] and one case of allergic contact dermatitis [2] have been reported from exposure to HBTU. Also, a case of occupational rhinitis with asthma has been described in a research scientist sensitized to HBTU [3].

We report on a laboratory worker who developed anaphylaxis and contact urticaria from airborne exposure to powdered HBTU.

Case report

Occupational exposure and symptoms

The patient was a 28-year-old man who had worked as a university laboratory worker for the past 3 years. The laboratory synthesized peptides, using various chemical agents, such as f-moc amino acids and HBTU. The work tasks of the patient included weighing of these substances which were in powder form. He did not use a respiratory mask or protective gloves.

In his past medical history, the patient had had atopic dermatitis in his childhood. He was allergic to nuts, and for this reason had once been hospitalized because of severe dyspnoea. He had also had allergic rhinitis to birch pollen since his early 20s, and respiratory symptoms related to contacts with horse and cat. Skin prick tests (SPTs) had shown allergy to pollens of birch, hay and alder, and epithelia of horse, dog, cat and cow. The patient was an ex-smoker. Two years earlier, he had been examined for dyspnoea presenting while playing floorball, and exercise-induced asthma was diagnosed by peak expiratory flow (PEF) measurements, treated with salbutamol as required. After these examinations, however, the patient had not had asthmatic symptoms, but he had been on continuous antihistamine medication because of rhinitis.

One year prior to being seen at the Finnish Institute of Occupational Health (FIOH), when weighing HBTU, the patient experienced redness and a burning sensation on his face associated with dyspnoea and faintness. He immediately contacted the occupational health unit, and 1 min later, the physician observed the skin symptoms; the patient’s lung auscultation was normal. He received antihistamine medication orally and was under medical observation for 2 h. After that he had weighed the HBTU in a fume cupboard. Six months later, when weighing large amounts of HBTU, the patient again experienced redness on his face, cough and dyspnoea. He also felt dizzy, and there was redness of the flexural areas of the extremities and on his chest. At the occupational health unit, the physician observed shallow respiration...
and urticaria on the patient's face and on the flexural areas on his extremities; the palms of his hands were also swollen. No respiratory wheezing was present on auscultation, and there was no laryngeal oedema, but the patient felt faint. He received intramuscular corticosteroid and peroral antihistamine medication, and was sent to an emergency unit of the local university central hospital for medical observation, where his symptoms subsided. Since then, the patient has not used HBTU and has been well. An adrenalin injection was added to the first aid kit at the workplace.

Investigations at the Finnish Institute of Occupational Health

When seen at the FIOH, the patient's skin was normal. SPTs were performed as described previously [4]. Allergic reactions were seen to birch pollen (5 mm), alder pollen (7 mm + pseudopodia), hay pollen (5–6 mm), horse (10 mm + pseudopodia), dog (7 mm) and cat (19 mm); histamine 10 mg/ml was 6 mm (positive control). SPTs with f-moc amino acid at concentrations of 0.01, 0.1 and 1% in a water/ethanol solution were negative. SPT with HBTU at a concentration of 0.1% (in aqua) gave a positive reaction (12 mm + pseudopodia). Both solutions were prepared from substances received from the workplace. A skin provocation test (i.e. open application test) with a concentration of 0.1% HBTU was negative, but with a concentration of 1% one urticaria wheal (diameter 4 mm) appeared within 20 min of observation. The test with the latter concentration was considered positive.

The patient had no respiratory symptoms, and lung auscultation was normal. X-rays of the chest and sinuses were normal. Flow-volume spirometry was normal [FVC 6.80 l (112%), FEV1 5.10 l (98%)] without bronchodilation effect [5]. In the histamine challenge test, a mild bronchial hyperresponsiveness was noted (PD_{15} 1.56 mg) [6]. The concentration of exhaled nitric oxide (NO) was 72.5 ppb, i.e. a clearly raised value [7]. PEF measurements during working days and days off without medication were performed according to the method of Burge [8]. They were recorded every 2 h from waking to sleeping on each day, and the monitoring time was 18 days including 6 days off. PEF measurements were 640–670 l/min when the patient had not handled HBTU; during the follow-up, the patient had not needed salbutamol medication. Diurnal PEF monitoring was also performed with salbutamol inhalations in the morning and in the evening; the measurements were normal (640–670 l/min), and no bronchodilating effects were seen.

Based on the clinical picture and positive SPT to HBTU, as well as positive skin provocation test with this chemical, the diagnoses of IgE-mediated occupational anaphylaxis and allergic contact urticaria due to occupational exposure to HBTU were made. Because our patient did not have lower respiratory symptoms pointing to work-related asthma and because the two anaphylactic reactions were his only work-related symptoms, no diagnosis of occupational asthma was made at the FIOH, but he had the previous diagnosis of exercise-induced asthma. Because of the noted bronchial hyperresponsiveness and high NO level in the exhaled NO test at the FIOH, inhaled corticosteroid medication for his asthma was prescribed for regular use. Furthermore, a prescription for intramuscular adrenalin injection (EpiPen Autoinjection®) on demand use was given. It was recommended that the patient should avoid all exposure to HBTU chemical and that the occupational hygiene situation at his worksite should be assessed. The case was reported to the Finnish National Register of Anaphylaxis.

Discussion

Anaphylaxis is a life-threatening syndrome with no universally accepted clinical description [9], although recently the World Allergy Organization has issued a revised nomenclature for allergic reactions [10]. According to a review by Kempf and Lockey [9], it consists of some or all of the following signs and symptoms: diffuse erythema, pruritus, urticaria and/or angioedema; bronchospasm; laryngeal oedema; hyperperistalsis; hypotension and/or cardiac arrhythmias. Other symptoms may additionally occur, such as nausea, vomiting, headache, lightheadedness, feeling of impending doom and unconsciousness. Of these, our patient met urticaria both as a symptom and as a sign, and also symptoms related to bronchospasm, hypotension and lightheadedness. Anaphylaxis can be caused by different pathophysiological mechanisms. The World Allergy Organization recommends that when the reaction is mediated by IgE antibodies, it should be referred to as IgE-mediated allergic anaphylaxis, because other immunological mechanisms, such as IgG- or complement-related ones also exist [10]. People with an atopic constitution are more prone to get an anaphylactic reaction than people without it.
Foods and medications have caused most of the anaphylaxis cases for which a cause can be identified [9]. In an occupational context, anaphylaxis has been reported to be caused by natural rubber latex, enzymes, animal proteins and drugs [9,11,12].

Our atopic patient, who was occupationally exposed to HBTU, had systemic urticaria and respiratory symptoms consistent with anaphylaxis, but a full-blown clinical picture did not develop, possibly reflecting the fact that he had been able to rapidly contact the occupational health unit, which was located near his workplace. Also, the continuous antihistamine medication which he used might have had some effect. The fact that our patient had a positive SPT to HBTU, implying that the reaction was IgE-mediated, supports the diagnosis of an allergic anaphylactic reaction. He also had immediate allergic contact urticaria, which was verified by a skin provocation test.

With regard to occupational exposure to HBTU, occupational contact urticaria has been previously reported in a 29-year-old female research scientist who had eye and respiratory symptoms [1]. She had positive SPT reactions not only to HBTU but also to HATU (N-(7-azabenzotriazole-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate), which is chemically related to HBTU and is also used in solid-phase peptide synthesis. Furthermore, occupational asthma with rhinitis has been described in a 30-year-old male pharmaceutical plant worker [3]. In line with the case report by Yung et al. [1], he also had an IgE-mediated hypersensitivity Type I reaction to HBTU, as shown with a positive SPT reaction. The occupational rhinitis was confirmed by a positive nasal challenge test, but a bronchial challenge test was not carried out. The diagnosis of occupational asthma was based on his respiratory symptoms with a positive nasal challenge test. Interestingly, he also had a positive prick test for TBTU (o-(benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium tetrafluoroborate), which is the coupling reagent of choice for HBTU. The nasal challenge test with TBTU was also positive. The third reported case (a 37-year-old male researcher in chemistry) displayed a clinical picture of occupational airborne allergic contact dermatitis due to HBTU [2]. Patch tests were positive but SPTs negative, so the mechanism involved was a hypersensitivity Type IV reaction, as the clinical picture of contact dermatitis indicated. Other chemicals which share the capability to induce both hypersensitivity Type I and Type IV reactions, as has been documented with HBTU, include acid anhydrides [13], di-isocyanates [14], epoxy resins [15] and methacrylates [16].

In conclusion, our results confirmed the previous observation that HBTU can induce IgE-mediated occupational contact urticaria, but they also pointed out that a severe potentially life-threatening condition, anaphylaxis, may occur. The previous case reports and our case show that HBTU is a chemical that may induce varied clinical allergic conditions, including allergic contact dermatitis, asthma, rhinitis, contact urticaria and even anaphylaxis. Therefore, this chemical should be handled with appropriate precautions as for known sensitizers. Finally, if occupational symptoms develop, we recommend that the worker should be transferred to other work tasks as soon as possible.

Conflicts of interest
None declared.

References

