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LETTER

Respiratory and skin hypersensitivity reactions caused by a peptide coupling reagent

TBTU (2-[1H-benzotriazol-1-yl]-1,1,3,3-tetramethyluronium tetrafluoroborate; CAS No: 125700-67-6) and HBTU (2-[1H-benzotriazol-1-yl]-1,1,3,3-tetramethyluronium hexafluorophosphate; CAS No: 94790-37-1) are increasingly used as coupling reagents for the stepwise synthesis of peptides. There have been isolated reports describing the development of rhinitis, urticaria and contact dermatitis¹⁻⁴ caused by these uronium compounds.

We evaluated six workers exposed to TBTU in a laboratory producing a wide variety of biologically active peptides. Three times a week, they weighed 30–50 g of TBTU powder into separate aliquots which were dissolved in dimethylformamide in closed vials and connected to an automated synthesiser. The survey included a detailed questionnaire and skin-prick tests with five common inhalant allergens, natural rubber latex, and freshly prepared dilutions of TBTU, HBTU and hydroxybenzotriazole (HOBt) (1 and 10 mg/ml) in sterile saline. The protocol of the study was approved by the hospital Ethics Committee.

One employee reported work-related asthma and rhinitis, while three others experienced both rhinitis and skin symptoms

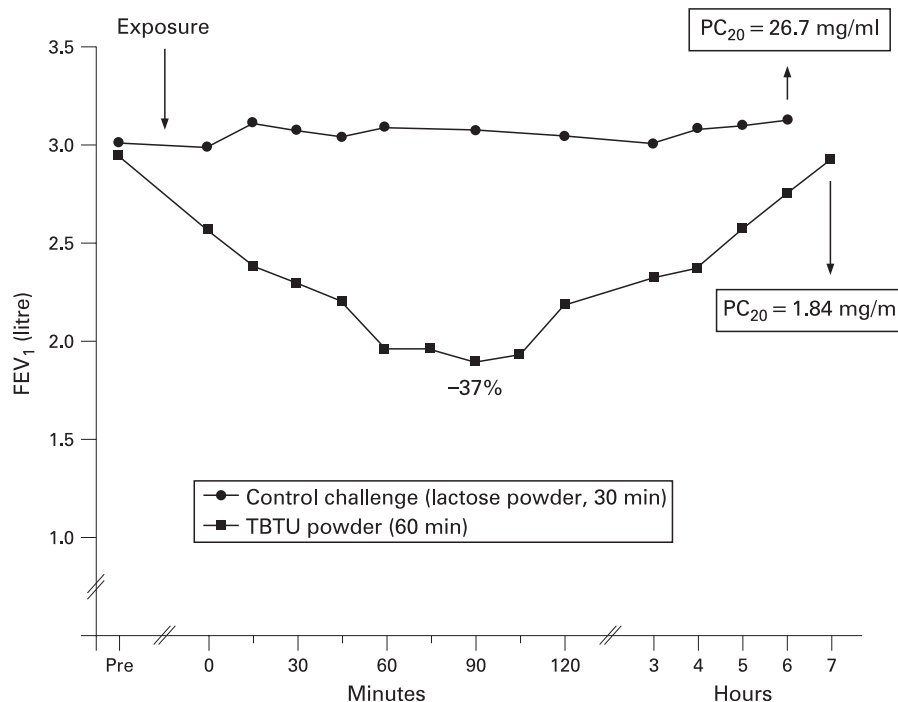


Figure 1 Results of bronchial provocation tests illustrating the changes in FEV₁ after exposure to lactose powder for 30 min (closed circles) and to TBTU (20 g diluted 1/10 in lactose) for 60 min (closed squares). PC₂₀ is the concentration of histamine causing a 20% fall in FEV₁.

(transient urticarial rash of the hands and face and persistent eczematous-like skin lesions on the hands). The nasal and skin symptoms

markedly decreased after improvement in the plant ventilation system, isolation of the weighing procedure, and implementation of stringent work practices (systematic cleaning procedures, use of respiratory protective masks for weighing operations, protective clothes changed daily, use of long-sleeved gloves).

These four symptomatic workers showed an immediate skin-prick test response to TBTU (table 1) but not to saline solution (negative control). Three of them also demonstrated a positive skin reaction to HBTU, while skin testing with HOBt gave negative results. Skin-prick tests with TBTU, HBTU and HOBt were negative in nine unexposed control subjects. Specific IgE antibodies against TBTU and HBTU conjugated to human serum albumin could not be detected in symptomatic workers using the ImmunoCAP technique (personal communication from L Strömbeck, Phadia Diagnostics, Uppsala, Sweden). The subjects did not agree to perform patch-testing with TBTU.⁴

Those employees who experienced work-related respiratory symptoms were offered the opportunity of further investigations (table 1). In the employee reporting work-related asthma, bronchial provocation challenge by tipping TBTU powder elicited an immediate asthmatic reaction and a significant increase in non-specific bronchial responsiveness to histamine (fig 1). Analysis of induced sputum showed an increase in the percentage of sputum eosinophils (6.3% of 5.32×10⁶ cells/ml) at 24 h post-challenge vs 0.3% of 1.89×10⁶ cells/ml in the control day sample). Nasal challenge with TBTU was carried out in only

Table 1 Clinical, immunological and functional characteristics of surveyed workers

	Subject no.					
	1	2	3	4	5	6
Age	28	30	25	24	49	53
Sex	F	M	M	F	F	M
Total duration of exposure to TBTU, months	55	18	27	37	95	100
Duration of exposure before onset of symptoms, months	31	3	8	2	NA	NA
Smoking habits	N	E	N	N	N	N
Atopy*	–	–	–	+	ND	ND
Work-related symptoms						
Skin	–	+	+	+	–	–
Rhinitis	+	+	+	+	–	–
Conjunctivitis	–	–	–	–	–	–
Asthma	+	–	–	–	–	–
Prick-testing						
TBTU, mg/ml	1	1	1	1	–	–
HBTU, mg/ml	1	–	1	10	–	–
HOBt, mg/ml	–	–	–	–	–	–
FVC, % predicted	106	102	97	103	ND	ND
FEV ₁ , % predicted	106	108	98	94	ND	ND
Histamine PC ₂₀ , mg/ml	0.35/26.7†	>16	>16	>16	ND	ND
Challenge with TBTU						
Bronchial	+	ND	ND	ND	NA	NA
Nasal	NA	ND	ND	+	NA	NA

E, ex-smoker; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; HBTU, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HOBt, hydroxybenzotriazole; N, never smoker; NA, not applicable; ND, not done; PC₂₀, concentration of histamine causing a 20% fall in FEV₁; TBTU, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate.

*Atopy defined as a positive skin-prick response to at least one of five common inhalant allergens.

†PC₂₀ values measured 3 and 20 months, respectively, after removal from exposure to TBTU.

one of the three employees reporting isolated work-related rhinitis (table 1). Instillation of the 1.0 mg/ml solution of TBTU induced complete blockage of nasal cavities and an increase in nasal lavage fluid eosinophils (from 0% post-saline to 20.5% in the sample collected 4 h after TBTU instillation).

The results of bronchial challenge with TBTU were consistent with those reported in asthmatic reactions induced by low-molecular weight agents, although the underlying mechanisms remain largely uncertain.⁵ Thus, the bronchial response to TBTU was associated with a significant increase in non-specific bronchial hyper-responsiveness and in sputum eosinophils. Immediate skin-prick test response to TBTU and HBTU supported a type I allergic response directed against these agents. Specific IgE antibodies could not be detected, which is often the case in workers with occupational asthma caused by low-molecular-weight agents.⁵ The nature of skin symptoms was consistent both with urticaria resulting from type I allergy and with allergic contact dermatitis due to delayed type IV hypersensitivity. The potentiating effects of

other chemicals present in the workplace, such as dimethylformamide, should be further explored.

These findings indicate that uronium salts have a high potential for inducing respiratory and skin hypersensitivity reactions. Stringent work hygiene programs should be implemented to minimise airborne and skin exposure to peptide coupling reagents. Exposed workers should be carefully observed for the development of respiratory and skin symptoms.

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