

Asthma due to 'glycyl compound' powder— an intermediate in production of salbutamol

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Introduction

Salbutamol, a selective β_2 -adrenergic bronchodilator, has been used in the U.K. since 1969 and is well tolerated over a wide dose range (Paterson & Shenfield, 1974). There have been no reports of allergic reactions to salbutamol itself.

In this paper we present the findings in an industrial process worker on the salbutamol production line who developed bronchial asthma as a result of exposure to 'glycyl' compound, 2-(N-Benzyl-N-tert-butylamino)-4'-hydroxy-3'-hydroxymethylacetophenone diacetate, an intermediate chemical powder prepared during manufacture.

Case history

The subject, a 48-year-old man at the time of investigation, first developed bronchial asthma at the age of 46. He gave no history of allergic disorders or chest symptoms before that time and there was no family history of allergies. He had smoked thirty cigarettes a day for most of his adult life until aged 47.

He started work on the salbutamol production line in 1970 at the age of 44, and first noticed wheezing and nocturnal dyspnoea in the spring of 1972. When first seen at hospital for this in January, 1973, there was no audible wheezing but his peak flow rate was 345 l/min, 56% of predicted normal. His symptoms continued intermittently until May, 1974 when he was admitted to hospital after a severe attack of asthma. His peak flow rate was 120 l/min, 19% of predicted. Sputum and blood eosinophilia was present at the time but prick tests were negative. He improved after salbutamol therapy.

He first noticed an association between attacks of asthma and work exposure to 'glycyl compound' in September, 1974. Symptoms started about 3 hr after exposure and persisted through the night. None of the other powders handled at work affected him. Treatment with prophylactic sodium cromoglycate was thought to be of little or no benefit and eventually he was given prednisolone to control his symptoms.

He was admitted to hospital for bronchial challenge testing in 1975 and all drugs were stopped.

Cospondence: Professor J. Pepys, Cardiothoracic Institute, Brompton Hospital, London SW3.

Physical examination revealed only a mild expiratory wheeze. Chest X-rays showed old healed tuberculosis in the left upper zone. Skin testing to twenty-three common allergens was negative and there was no eosinophilia in blood and sputum. Prick tests with 'glycyl compound', 'benzyl compound' and salbutamol at 1 mg/ml and 10 mg/ml were negative. His lung function tests showed a moderate obstructive defect with a normal gas transfer.

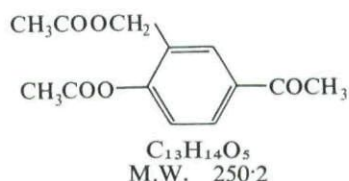
FEV₁ 1950

FVC 4590

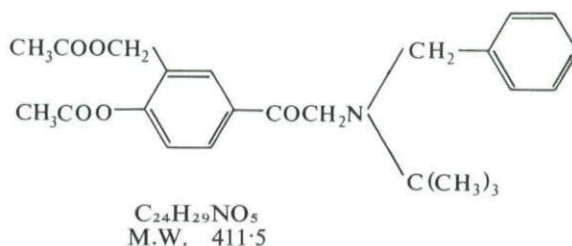
$$\frac{\text{FEV}_1}{\text{FVC}} = 42\%$$

The salbutamol production process

The production starts with 'diacetate' 4'-hydroxy-3'-hydroxymethylacetophenone diacetate,

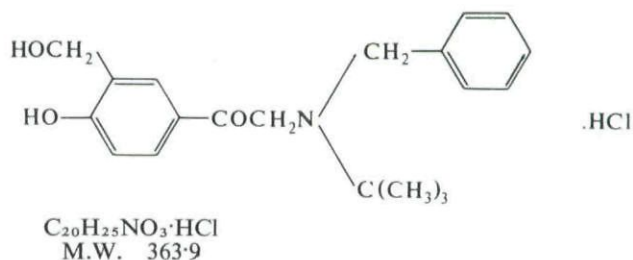


which is a waxy powder and a series of reactions produces in turn 'glycyl compound',



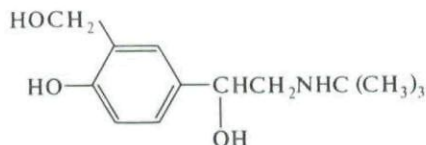
2-(N-Benzyl-N-tert-butylamino)-4'-hydroxy-3'-hydroxymethylacetophenone diacetate

benzyl compound,



2-(N-Benzyl-N-tert-butylamino)-4'-hydroxy-3'-hydroxymethylacetophenone hydrochloride

and salbutamol



α -tert-butylaminomethyl-4-hydroxy-m-xylene-
 α, α' -diol

which are isolated as powders. After being oven dried, the powders are tipped from trays into metal kegs inside a chamber approximately 336 cu. ft in volume, fitted with an extractor fan. The process is dusty and the workers wear a Martindale mask with two pad filters. After the job they change their outer clothes and have a shower.

Bronchial challenge tests

The following tests were carried out with samples of the chemical powders isolated in manufacture using the technique described by Pepys, Pickering & Loudon (1972) in which dried lactose powder is used as a vehicle and shaken repeatedly between two trays. This provides a fine powder in the atmosphere. Test substances can be added to the lactose and tests carried out single blind.

Tests

- (1) Lactose powder 250 g—control.
- (2) Glycyl compound 100 mg + lactose 250 g.
- (3) Benzyl compound 100 mg + lactose 250 g.
- (4) Diacetate 100 mg + lactose 250 g.
- (5) Salbutamol 100 mg + lactose 250 g.
- (6) Glycyl compound 100 mg + lactose 250 g after pre-treatment with 40 mg sodium cromoglycate.
- (7) Glycyl compound 100 mg + lactose 250 g after pre-treatment with 200 μ g beclomethasone dipropionate.
- (8) Glycyl compound 100 mg + lactose 250 g after pre-treatment with beclomethasone dipropionate placebo.

Results

These are illustrated in Figs 1–3. The control test (1), diacetate (4), and salbutamol (5), gave no significant reaction.

Glycyl compound (2) produced a late asthmatic reaction starting at 2 hr and maximum at 4.5 hr which did not fully recover till 24 hr after challenge. This reaction was not inhibited by sodium cromoglycate (6) but was partially inhibited by beclomethasone dipropionate (7).

Discussion

The occupational method of exposure reproduced this man's symptoms and confirmed the clinical history. Approximately eighteen workers were exposed to this powder but only one other had symptoms; unfortunately he was not available for testing. The marked reaction to a small dose in this man tends to favour an allergic hypothesis but we have not sought immunological evidence to support this. The mild late reaction

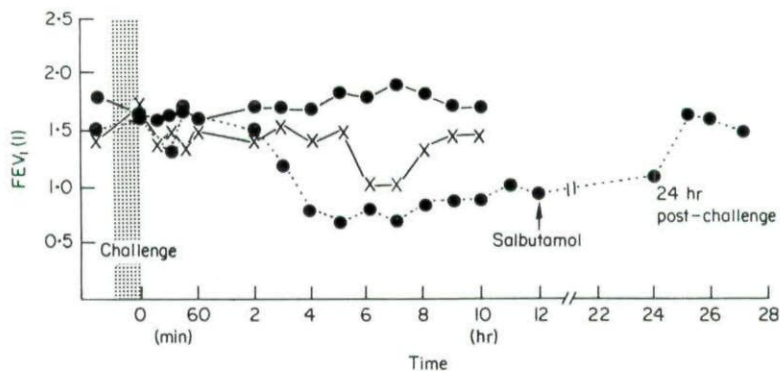


Fig. 1. Non-immediate asthmatic reaction to glyceryl compound and a weaker reaction to benzyl compound. ●—●, Lactose control; ●····, glyceryl compound test; X—X, benzyl compound test.

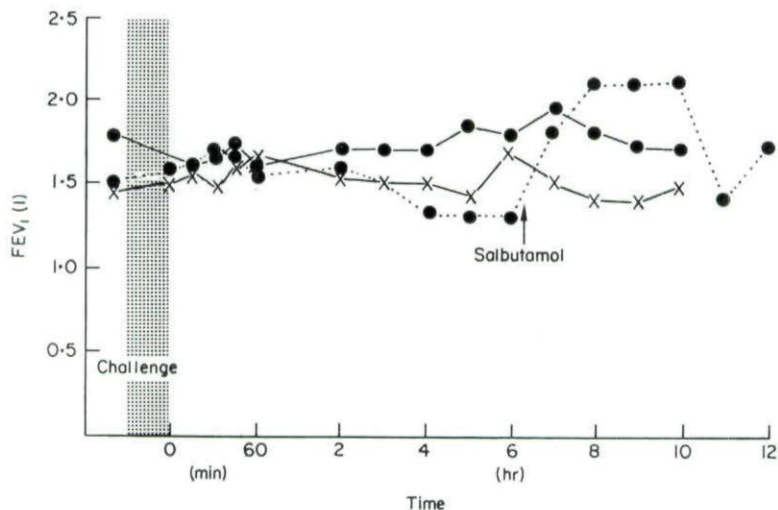


Fig. 2. No reaction to diacetate. ●—●, Lactose control; X—X, diacetate test; ●····, Salbutamol test. Note bronchodilator effect.

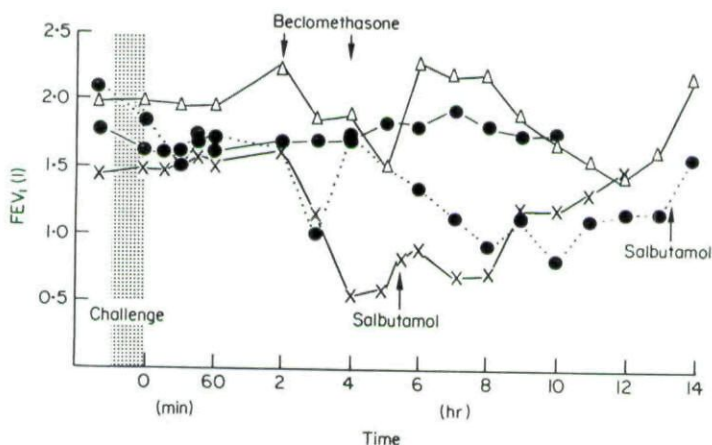


Fig. 3. Blocking of reaction by inhalation of beclomethasone dipropionate given 2-hourly but not by pre-treatment with sodium cromoglycate. ●—●, Lactose control; X—X, glyceryl test; △—△, glyceryl test + beclomethasone 2-hourly; ●····, glyceryl test + beclomethasone placebo 2-hourly.

to the next powder in the production sequence, the 'benzyl' compound may reflect structural similarity or perhaps the carry over of an impurity.

Salbutamol, the end product of the process, was always effective in varying degree in reversing his bronchial obstruction.

Acknowledgment

We would like to thank Dr B. L. D. Phillips, Company Medical Officer, Allen & Hanburys Ltd, Ware, Hertfordshire for information regarding the preparation of salbutamol.

References

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