calibrating the Eyetone was perhaps a significant factor in our patient's choice. For hospital use a mains-operated monitor is usually desirable. Our electronics engineer gave marginal preference for Eyetone. Reflomat, however, has a potential advantage in that the Reflotest system holds its colour and reading, which could be an advantage under certain circumstances.⁴ Both the Eyetone and the Reflomat gave good results. Our experience with Eyetone monitors over several years has been favourable and the after-sales service excellent.

For self-monitoring, however, further advances in technology are expected. The BM-Test-Glycémie 20-800 strip (Boehringer) now available is yielding encouraging results and may provide a system of monitoring without the need for an actual monitor. Nevertheless, of the four monitors currently available our triple assessment of patient preference, laboratory performance, and electronic opinion gave first place to Hypocount.

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Protective effect of inhaled salbutamol powder in children assessed by histamine challenge

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Summary and conclusions

A double-blind placebo-controlled trial of 100, 400, and 800 µg inhaled salbutamol powder was conducted on 12 children. The protective effect at 10 minutes, two hours, and four hours was assessed by histamine challenge. At 10 minutes there was good protection with all doses, but by four hours there was significant protection only with 800 µg ($p < 0.01$). Salbutamol powder may need to be taken at least every four hours for complete protection. There was a dose-related effect with a single dose of up to 800 µg; increasing the dose increased the effect and duration of action.

Currently advertised dose regimens of salbutamol powder for children (200 µg three or four times a day) are apparently submaximal. Histamine challenge is a satisfactory method of assessing the protective effect of a drug in asthmatic children.

Introduction

Inhaled salbutamol is well established as a valuable treatment of wheezing in children.¹ Many young children have difficulty mastering the metered aerosol² but can use a dry powder inhaler.³ Young children unable to use a metered aerosol who require inhaled salbutamol have had to use air compressors to drive nebulisers, which are both cumbersome and expensive.

Salbutamol powder is now available for use in an inhaler (Rotahaler, Allen and Hanburys). This effectively increases the forced expiratory volume in one second (FEV₁) in adults^{4,5} and children.⁶ The recommended prophylactic dose is 400 µg for adults and 200 µg for children three or four times a day. This dose, however, may produce submaximal responses in

children,⁶ and Hetzel and Clark⁵ reported increasing effect in adults with cumulative doses of up to 800 µg. Many children with asthma have intermittent wheezing with a normal FEV₁ for much of the time.⁷ Hence testing a single dose of a drug and its effect on FEV₁ can be done only on a few more severely affected children. In the other cases, however, episodes may still be frequent enough to warrant continuous treatment with salbutamol.

Histamine is a non-specific bronchoconstrictor in increased bronchial lability.^{8,9} It is useful in assessing the protective effect of drugs, since the bronchoconstriction can be controlled and its effect is transient.¹⁰ We decided to assess the protective effect of a single dose of salbutamol powder using inhaled histamine. The trial was approved by the local ethical committee.

Subjects and methods

Twelve children aged 6-13 years with episodic asthma were studied. All could perform satisfactory forced expiratory manoeuvres. Eleven had a baseline FEV₁ of 70% or more of the predicted normal value on each day (normal values taken from Cogswell *et al.*¹¹). One boy had an FEV₁ of 58% predicted on one day and between 70% and 90% on the other days. Only steroids were continued from 12 hours before the start of each study day until after the last histamine challenge of that day.

Histamine challenge—The histamine challenge procedure used was similar to that of Chai *et al.*¹² FEV₁ was recorded on a Vitalograph. When consistent results were obtained the best of three was used as a baseline. Buffered histamine acid phosphate was used in roughly doubling concentrations from 0.03 mg/ml to 10 mg/ml. Solutions were administered by facemask from a Bard Mini-Neb nebuliser driven by oxygen at 8 l/min. Five inspiratory capacity breaths were taken first of diluent alone, and three minutes later the FEV₁ was recorded. Provided there was no fall in FEV₁ with the diluent this was repeated with increasing concentrations of histamine at four-minute intervals until the FEV₁ had fallen by 20% or more. The test was then stopped. The concentration of histamine that would produce a 20% fall (provocation concentration 20; PC₂₀) was calculated from the dose-response curve. If the FEV₁ did not fall by 20% with the top concentration (10 mg/ml) a PC₂₀ was calculated by extrapolation up to 20 mg/ml, but not beyond.

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Salbutamol powder trial—Each of the 12 children was studied on four separate days within two weeks. Salbutamol and placebo cartridges were administered by Rotahaler in the following combinations: (1) placebo+placebo, (2) placebo+100 µg, (3) placebo+400 µg, (4) 400 µg+400 µg. Cartridges were given double-blind in an order determined by the Latin-square design. A baseline histamine challenge was carried out at 9 am each day and the PC₂₀ established. The cartridges were given two hours later. Histamine challenge was repeated at 10 minutes, two hours, and four hours after administration of the cartridges and a new value for PC₂₀ obtained. Pulse rate was taken before and 10 minutes after the cartridges were given.

Statistical—The increase from baseline of log₁₀ PC₂₀ was calculated and significance of differences between doses estimated by paired *t* tests.

Results

Eight children had a baseline PC₂₀ that remained within three consecutive concentrations of histamine solution, but three children varied by four concentrations and one by five. There was no statistically significant difference between the mean baselines for all 12 children with each dose (*p* > 0.2). During the day when placebo was given the PC₂₀ with the baseline challenge was close to that of the last challenge of the day; 11 children varied by one concentration and one by two concentrations.

The figure shows the mean increase from baseline log₁₀ PC₂₀ in all 12 children with each dose at each time. At 10 minutes all salbutamol

Increase from baseline of log₁₀ PC₂₀ after inhalation of salbutamol and placebo powder.

doses gave significantly better protection than placebo (100 µg *p* < 0.05; 400 µg *p* < 0.005; 800 µg *p* < 0.005). At two hours there was still significant protection with all doses (100 µg *p* < 0.02; 400 µg *p* < 0.005; 800 µg *p* < 0.005), but there was a trend for enhanced protection with higher doses (100 µg *v* 400 µg *p* > 0.2; 400 µg *v* 800 µg *p* > 0.01; but 100 µg *v* 800 µg *p* < 0.02). By four hours there was no significant protection with 100 µg (*p* > 0.02) or 400 µg (*p* > 0.05), but there was with 800 µg (*p* < 0.01).

The increase in mean pulse rate after placebo was 4.0 (range × 8 to +16) beats/min, and after 100 µg 3.5 (range × 12 to +24) beats/min. Neither of these rises was significant. Mean pulse rate increased by 7.4 (range 0 to +24) beats/min 10 minutes after 400 µg salbutamol (*p* < 0.05) and by 9.5 (range × 4 to +24) beats/min after 800 µg (*p* < 0.05).

Discussion

Salbutamol dry powder effectively raised the threshold of sensitivity to histamine challenge. A pilot study on seven children showed significant difference between 200 µg and 400 µg at 30 minutes, three hours, and six hours, so 100 µg was chosen to see if it was equally effective and 800 µg to investigate the possibility of a greater effect with higher doses.

All doses of salbutamol gave satisfactory protection at 10 minutes. Some discrimination between the doses was lost because several children had a PC₂₀ exceeding 20 mg/ml, but all these were counted as 20 mg/ml. There was a definite though small placebo response at 10 minutes, but this had disappeared at two hours. The benefit of the larger doses was seen in their

duration of action. There was evidence of a dose-related effect, though the difference between only 100 and 800 µg reached significance. By four hours only 800 µg gave significant protection. This suggests that higher doses may benefit some children who get suboptimal or brief benefit from the standard dose. Although the mean pulse rate increased after 400 and 800 µg, this never caused concern and there were no subjective side effects. We have no information on side effects with regular use of higher doses.

Although some protection against histamine-induced bronchoconstriction remained at four hours with 800 µg, it was much reduced. Children who require regular treatment with salbutamol powder may need to take it at least every four hours.

Histamine challenge was well tolerated by all children. The fall in FEV₁ was generally between 20% and 30%, and any tightness in the chest was gone within 10-20 minutes. There was baseline variability, but there was no evidence of a cumulative effect or tolerance when histamine challenge was repeated every two hours. Sensitivity to histamine is consistent in adults over a short period⁸ but may vary with season¹³ and time of day.¹⁴ Histamine challenge therefore constituted a useful method of assessing the response of asthmatic children to the protective effect of a drug and its duration of action.

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ONE HUNDRED YEARS AGO M Georges Herbelin, a medical student at the Hôpital St Eugénie in Paris, was buried on Tuesday last with well-deserved honours. The young man, whose courageous devotion to the sick had won the admiration of the hospital authorities, caught diphtheria while tending a little girl suffering from that terrible malady. Before dying, the brave student had the satisfaction of receiving the Cross of the Legion of Honour, which was taken to him on his deathbed, and which he clasped to his breast as he expired. M Lepère, Minister of the Interior, M Herold, the Prefect of the Seine, several municipal councillors, and a number of leading physicians and medical students, attended the funeral. A detachment of infantry rendered him military honours. Several speeches by Professors of the Faculty were made over his grave. It is remarkable that the father of the deceased, who was a medical man, lost his life in the same way. (*British Medical Journal*, 1880.)