procedure for climacteric women receiving hormone replacement therapy or to monitor the reversal of endometrial hyperplasia with oral progestogens.[8] One cytologist felt that a confident diagnosis was possible only when a piece of endometrial tissue had been obtained, allowing a histological diagnosis to be made.

We believe that cytology will not be a useful means of detecting endometrial abnormalities and that efforts should be directed towards establishing the correct dose and duration of treatment with an oestrogen-progestogen preparation to avoid overstimulating the endometrium.

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Comparison of salbutamol given intravenously and by intermittent positive-pressure breathing in life-threatening asthma

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Summary and conclusions

A double-blind crossover trial was carried out during 22 episodes of life-threatening asthma in 19 patients to compare salbutamol given as a 500 μg intravenous injection and as a 0·5% solution administered by intermittent positive-pressure breathing (IPPB) for three minutes. Relief of pulsus paradoxus was significantly better after IPPB than the intravenous treatment. Both treatments significantly improved the peak expiratory flow rate. Salbutamol given intravenously produced a mean increase in heart rate of over 20 beats/min five minutes after treatment compared with the relief of tachycardia that occurred after administration by IPPB. Four patients had noticeable cardiovascular side effects after salbutamol given intravenously, but no such effects were noticed after administration by IPPB. Two patients withdrawn shortly after entry into the trial because of a worsening clinical condition had received intravenous salbutamol.

It is concluded that salbutamol given by IPPB is better than that given by slow intravenous injection in severe acute asthma.

Introduction

Bronchodilators are essential in treating severe acute asthma in the critical initial period before corticosteroids have had time to act. Beta$_2$-stimulant drugs such as salbutamol or terbutaline may be given intravenously or as an aerosol via a nebuliser with or without the additional help of intermittent positive-pressure breathing (IPPB). The best route of administration in the severely ill patient is still controversial, and we designed this study to compare the efficacy of salbutamol given by IPPB and by intravenous injection.

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Patients and methods

All patients who entered the trial had severe acute asthma and satisfied the criteria of having a heart rate of over 120 beats/min and a peak expiratory flow rate (PEFR) less than 20% of the predicted normal. All patients gave their informed consent. The trial was a double-blind crossover comparison of two treatments given one hour apart, the order of treatment being randomly allocated. The treatments were (1) a 0·5% solution of salbutamol given for three minutes by IPPB, plus 5 ml of saline given by intravenous injection over three minutes; and (2) saline given for three minutes by IPPB, plus 500 μg salbutamol in 5 ml saline given by intravenous injection over three minutes. A patient-triggered Bennett ventilator with a tightly fitting face mask was used to deliver the nebulised solutions by IPPB. All patients also received 500 mg hydrocortisone intravenously and oxygen via 35% Ventimask.

When the patients entered the trial we measured the PEFR with a Wright peak flow meter, using a low-reading paediatric meter when necessary, and recorded the best of three attempts. The heart rate was read from a Hewlett-Packard cardiac monitor and the respiratory rate recorded. These measurements were repeated five, 15, 30, 45, and 60 minutes after each treatment. Arterial blood-gas analysis was made on entry at least five minutes after the patient had been inspiring 35% oxygen and repeated 60 minutes after each treatment. The degree of pulsus paradoxus was measured using a sphygmomanometer on entry and 60 minutes after each treatment.

We studied 22 episodes of severe acute asthma in 19 patients aged 17-54 years (mean 27·35 years). Nine of the patients were receiving prednisolone or adrenocorticotrophic hormone and inhaled corticosteroids as regular maintenance treatment; three were taking inhaled beclomethasone alone; and two were taking sodium cromoglycate alone. All except one patient had been using a sympathomimetic aerosol before admission, and one had used a Bennett ventilator to administer salbutamol by IPPB at home some 90 minutes before admission. Two patients were withdrawn from the trial within 30 minutes after entry and given conventional treatment when their

clinical condition worsened. The codes were not broken, however, and the treatment orders were subsequently reallocated. Two patients were studied more than once: one was entered into the trial three times and the other twice. Twenty treatment regimens were completed, the initial treatment being intravenous salbutamol in 10 cases and IPPB in 10.

Results

The group of patients who received salbutamol by IPPB as first treatment were comparable in all respects with those who received intravenous salbutamol first. Statistical analysis was carried out to compare these two groups using Student's t test and Wilcoxon's rank sum test, which gave comparable probability values. Allowance was made for the order effect in the crossover phase of the trial. For statistical purity in the analysis we used only the first trial recordings in those patients who were studied more than once. Analysis including the recordings obtained on subsequent admissions, however, gave similar results. No tests for interaction effects gave significant results.

Heart rate—Figure 1 shows the change in heart rate from the value before treatment. The mean rate on admission was 138 beats/min. Intravenous salbutamol caused an increase in mean heart rate over the first five minutes of more than 20 beats/min followed by a progressive fall, whether given as first or second treatment. In contrast, IPPB caused an immediate and progressive fall in heart rate when given as first treatment, and a small mean rise of 6 beats/min followed by a progressive fall when given second. This difference was highly significant at five minutes after each treatment ($P<0.005$). The heart rate remained significantly higher for 15 minutes after intravenous salbutamol than after salbutamol given by IPPB ($P<0.01$). It also remained higher after intravenous treatment at 30, 45, and 60 minutes, but this was not statistically significant ($P=0.1$).

PEFR—Figure 2 shows the results expressed as the increase in PEFR over the rate before treatment. The mean PEFR on admission was 103 l/min. After each treatment the mean rate had risen by at least 20 l/min above the value before treatment within five minutes, this difference being significant ($P<0.0005$). In the patients who received intravenous salbutamol followed by salbutamol by IPPB the final mean PEFR at two hours was 74 l/min higher than the rate at entry. In patients who received salbutamol by IPPB first the mean PEFR at two hours was 54 l/min higher than that on entry. A greater improvement occurred overall after salbutamol given by IPPB. There was no statistical difference, however, in the effect of either treatment or the order of treatment on PEFR.

Pulsus paradoxus—On entry the mean degree of pulsus paradoxus was 33·8 mm Hg. In the patients who received salbutamol by IPPB first the mean fall in pulsus paradoxus in the first hour was 13·6 mm Hg, while in the second hour (after intravenous salbutamol) the mean fall was 2·9 mm Hg. In those who received intravenous salbutamol first the mean fall was 9·2 mm Hg in the first hour, but 15·0 mm Hg after IPPB. These differences are significant ($P<0.05$).

Arterial blood-gas tensions—The mean arterial oxygen pressure on admission was 11·55 kPa (87 mm Hg) range 5·1-16·5 kPa; 38-124 mm Hg). The effect of treatment on oxygen pressure varied widely, with both large falls and rises. Mean rises of 0·74 kPa (6 mm Hg) occurred after salbutamol given by IPPB and of 0·62 kPa (5 mm Hg) after intravenous salbutamol, with no significant difference between the two treatments.

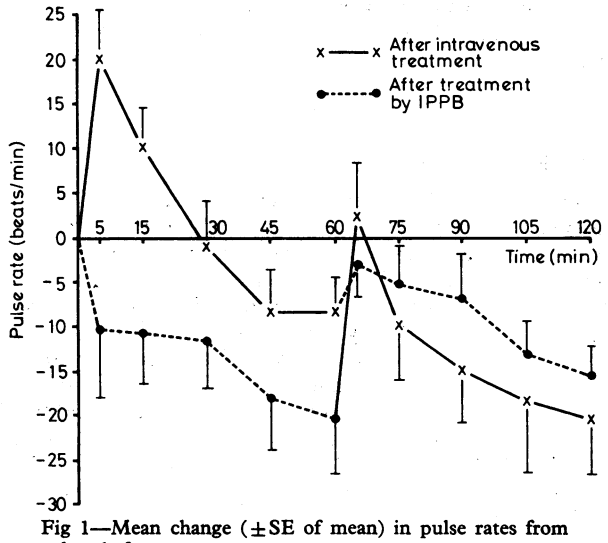

Fig 1—Mean change (±SE of mean) in pulse rates from values before treatment.

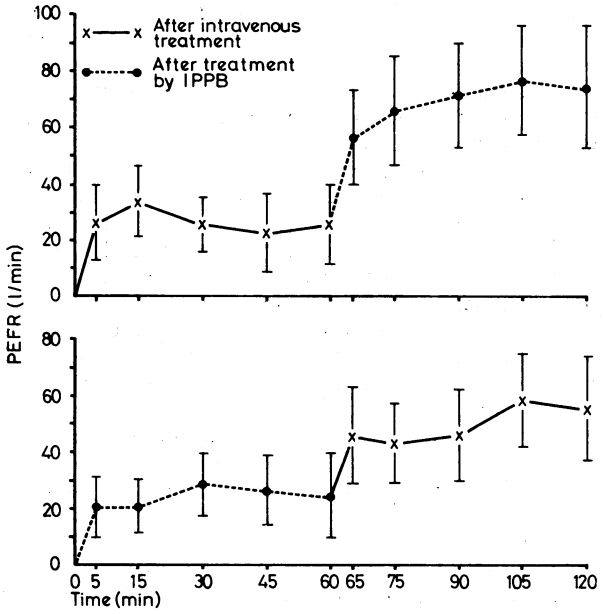

Fig 2—Mean change (±SE of mean) in peak expiratory flow rate (PEFR) from value before treatment.

Respiratory rate—The mean respiratory rate on entry was 27·5 breaths/min. After both treatments the rate fell progressively, the maximum mean falls being 4·25 breaths/min 45 minutes after salbutamol given by IPPB and 3·75 breaths/min 30 minutes after intravenous salbutamol. There was no significant difference between the two treatments.

Side effects and patients withdrawn—When the treatment code was broken after the study was completed, we found that the two patients withdrawn within the first treatment hour because of worsening clinical conditions had both received intravenous salbutamol. Both subsequently improved after our conventional treatment, which included salbutamol by IPPB. Four patients complained of shakiness, and two of these also experienced palpitations after the intravenous treatment. There were no side effects related to administration of salbutamol by IPPB.

Discussion

Objective assessment of treatment in patients who are severely ill is difficult, particularly in those with acute severe asthma.[1] It is much easier to compare different treatments in patients who have relatively mild episodes of asthma than in those who are extremely ill and require immediate intensive treatment. The optimum treatment for severely ill patients, however, cannot always be defined by extrapolating the results of clinical trials performed in patients with relatively mild disease, though there is often a temptation to do this.

Intravenous salbutamol is as effective as aminophylline and less likely to cause nausea and vomiting.[2] In a study in which inhaled and intravenous salbutamol were compared the intravenous preparation was no more effective in patients with stable asthma than salbutamol given by pressure-packed aerosol, and produced tremor and cardiovascular changes.[3] Lawford *et al*[4] concluded that in severely ill patients the drug given intravenously had disadvantages of tremor and tachycardia, effects not found with the nebulised preparation. Williams and Seaton[5] compared salbutamol given by IPPB and intravenously in severe asthma and concluded that the intravenous route was more effective, attributing this to mucus plugging preventing effective distribution of the nebulised drug.

Our results show that salbutamol given by IPPB is more effective in relieving pulsus paradoxus than salbutamol given by intravenous injection. Pulsus paradoxus in asthma reflects abnormal intrathoracic pressures produced by airways obstruction, and hence its relief is an important index of improvement. Direct measurement of airways obstruction using the PEFR indicated that significant relief occurred after both treatments but with no statistical difference between the two methods. It is difficult to explain why there was such a pronounced difference between the two treatments in relieving pulsus paradoxus but little difference in their effect on the PEFR. Pulsus paradoxus is a valuable sign indicating severe asthma and correlates well with other objective and clinical assessments.[6] Woolcock and Reid[7] showed that a reduction in lung volumes and a consequent reduction in the elastic work of inspiration after administration of bronchodilator drugs to patients with acute asthma may precede improvement in the forced expiratory volume. Our results suggest that relief of pulsus paradoxus may be a more sensitive index of improvement in acute asthma than simple measurements of ventilatory function such as PEFR and forced expiratory volume. We think it unlikely that the difference between treatments may be wholly explained by a direct cardiovascular effect of intravenous salbutamol. Previous trials of drugs in severe acute asthma have not used pulsus paradoxus as an objective index of response to treatment, and this may prove to be a useful measurement for similar trials in the future.

No undesirable side effects were reported by patients after administration by IPPB, but four patients had palpitations and tremor after they had been given salbutamol intravenously. Both patients withdrawn from the trial within the first treatment hour because of a worsening clinical condition had received intravenous salbutamol. Intravenous salbutamol induced a mean increase in heart rate of over 20 beats/min compared with the relief of tachycardia observed after the drug was given by IPPB. We used a large dose of intravenous salbutamol, but similar heart-rate responses have been recorded when lower doses have been given by intravenous injection, and also when the drug has been given by a constant infusion.[4 5 8]

We conclude that because of its greater efficacy and freedom from side effects 0·5% salbutamol administered by IPPB for three minutes is superior to 500 μg salbutamol given by intravenous injection over three minutes in treating patients with severe asthma.

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Changes in fatty-acid composition of body fat before and after birth in Tanzania: an international comparative study

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Summary and conclusions

Changes in the fatty-acid composition of human adipose tissue before birth and during infancy and childhood were studied in Tanzania and compared with data for British and Dutch infants in relation to their diet. From the 32nd to the 37th week of gestation in Tanzania the proportion in the body fat of the unsaturated fatty acid linoleic acid tended to rise, suggesting an adequate supply of this essential fatty acid from the mother to the fetus. At term 2·5% of the total fatty acids of the body fat was linoleic acid, which corresponded with values in Dutch newborn infants but was significantly higher than those in British infants. During infancy in Tanzania the composition of the fat showed a dramatic increase in the proportions of the saturated fatty acids lauric acid and myristic acid, which did not occur in Dutch and British infants. The proportion of linoleic acid increased to 8%. These changes were a reflection of the fatty-acid composition of the fat in the human milk that the infants received. During weaning (1-2 years of age) the fatty-acid composition changed only slightly.

The specific fatty-acid composition of the fat in Tanzanian breast milk may have a beneficial influence on the extent of intestinal absorption in the newborn child.

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Introduction

In Tanzania and the other developing countries of Africa the incidence of arteriosclerosis is low. Establishing a correlation between the quality and quantity of fat intake during childhood and the genesis of risk factors for arteriosclerosis in adult life is difficult, as is shown by the controversial findings of several studies.[1–5] Dietary fat in young infants not only serves as the most important source of energy but also contains nutrients essential for normal growth and development. The nature of the fat consumed in terms of the proportions of fatty acids and their different chain lengths can have an important influence on the fatty-acid composition of adipose tissue[6] and human milk fat,[7] but probably not on the composition of lipids in cell membranes and nervous tissue. Since diets are subject to custom as well as to socioeconomic circumstances, comparing the fatty-acid