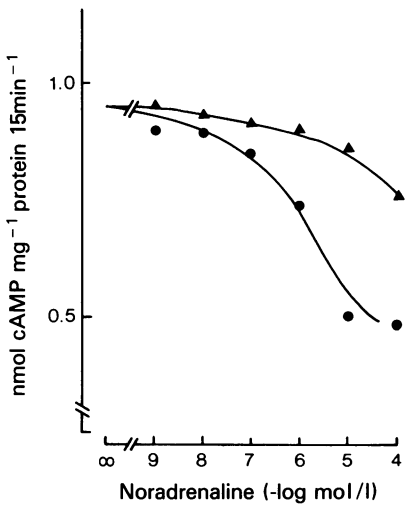

Figure 1 Inhibition of the human fat cell adenylate cyclase by the α-adrenergic component of noradrenaline.
Subcutaneous adipose tissue was from six surgical patients. Fat cells and fat cell ghosts were prepared according to Rodbell (1972). The adenylate cyclase activity was assayed according to Salomon *et al.* (1974) at 30°C, pH 8.0 and in the presence of 10 μmol/l GTP. The concentrations of propranolol and phentolamine were 5×10^{-5} and 10^{-5} mol/l respectively. ● Propranolol alone, ▲ propranolol plus phentolamine.

useful for screening the metabolic effects of adrenergic drugs as influenced by diet, age or disease.

H. KATHER, J. PRIES, V. SCHRADER & B. SIMON

Klinisches Institut für Herzinfarktforschung an der Medizinischen Universitäts Klinik Heidelberg. Bergheimerstraße 58, D-69 Heidelberg, West Germany.

Received June 18, 1979

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DOSE-TITRATION COMPARISON OF INHALED SALBUTAMOL AND ORAL THEOPHYLLINE IN ASTHMA

β-adrenoceptor agonists by inhalation and oral theophylline, both widely used in the treatment of chronic asthma, have been compared with respect to potency and duration of action in single dose studies (Hartnett & Marlin, 1976; Marlin, Hartnett, Berend & Hacket, 1978). However, for an accurate assessment of relative potency, the relationship of the dose of the drugs to their dose-response curves must be known. The value of establishing dose-response curves when comparing the bronchodilator potencies of drugs is well established (Shenfield & Paterson, 1973; Marlin, Hartnett & Berend, 1977; Marlin, Bush & Berend, 1978). The object of this study was to compare by dose-response curves the bronchodilator potency of salbutamol by pressurized aerosol and oral theophylline.

Eight patients, aged 32 to 78 years, with chronic, partially reversible airways obstruction due to chronic asthma, were selected for this study after their informed, written consent. Their baseline forced expiratory volume in one second (FEV_1) ranged between 29 and 56% of predicted normal and their % FEV_1 increase after 200 μg salbutamol by pressurized aerosol was between 20 and 65%. The

patients were receiving maintenance treatment with combinations of prednisone, theophylline, beclomethasone diproprionate and salbutamol by pressurized aerosol.

The study was performed on two consecutive days and there was less than 15% variation between control, baseline FEV_1 values. The salbutamol dose-response was performed on the first day by giving one inhalation (100 μg) and FEV_1 and pulse rate were recorded before and after at 15 min intervals until the FEV_1 either remained the same or decreased. A second inhalation was given with the same procedure repeated and subsequently two, four and eight inhalations were taken. The peak response after a salbutamol dose occurred between 15 and 45 min which meant that the time interval between doses ranged between 30 and 60 min. The total duration of the study was between 2.5 and 3.5 h during which time it was considered that the initial dose would still be active. The theophylline dose-response was performed on the second day by giving 250 mg orally (Nuelin, 125 mg/tablet, 3M Riker Laboratories) and two further 250 mg doses after 2 and 4 h. FEV_1 and pulse rate were recorded and serum theophylline levels measured by radioimmunoassay (Clinical Assays) before drug intake and at hourly intervals for 6 h. All theophylline derivatives were withdrawn for 7 days before the first study day, salbutamol aerosol for 12 h before each day, but corticosteroids were continued at their maintenance doses. The results were submitted to statistical analysis using the paired Student's *t*-test.

There was no significant difference between the control FEV_1 values before salbutamol (mean ± s.e. mean, 1.26 ± 0.11 litres) and theophylline (mean ± s.e. mean, 1.28 ± 0.13 litres). The mean ± s.e. mean peak % FEV_1 changes from control after salbutamol and theophylline are shown in Tables 1 and 2 respectively and the mean ± s.e. mean serum theophylline levels in Table 3.

The FEV_1 response after sixteen inhalations of salbutamol was significantly greater than those after all other doses ($P<0.01$), and the responses after four and eight inhalations were significantly greater than those after one and two inhalations ($P<0.05$). The FEV_1 theophylline responses at 4 and 5 h were significantly greater than those at 1, 2 and 3 h ($P<0.05$). The salbutamol responses with four, eight and sixteen inhalations were significantly greater than the theophylline response at 4 and 6 h ($P<0.05$) and the salbutamol responses with sixteen inhalations were significantly greater than the theophylline response at 5 h ($P<0.05$). There was a positive correlation between FEV_1 effect and log serum theophylline concentration ($r=0.51$, $P<0.001$). One patient reported nausea when his serum theophylline level was 91.7 μmol $litre^{-1}$. The mean ± s.e. mean pulse rate increases for salbutamol and theophylline were 1.75 ± 3.33 beats/min after sixteen inhalations and 2.50 ± 1.88 beats/min at 5 h respectively.

Table 1 The mean ± s.e. mean % FEV_1 changes from control for eight patients with chronic asthma after cumulative doses of one, two, four, eight and sixteen inhalations of salbutamol by pressurized aerosol.

	Cumulative dose (number of inhalations)				
	1	*2*	*4*	*8*	*16*
Mean (s.e. mean) % FEV_1 increase from control	22.5 (8.4)	30.9 (6.6)	38.7 (6.1)	42.5 (8.7)	51.7 (7.5)

Table 2 The mean ± s.e. mean % FEV_1 changes from control for eight patients with chronic asthma for 6 h after three 250 mg oral doses of theophylline administered at 0, 2, and 4 h

	Time (h)					
	1	*2*	*3*	*4*	*5*	*6*
Mean (s.e. mean) % FEV_1 increase from control	5.6 (3.1)	6.6 (2.8)	8.1 (5.0)	17.4 (4.5)	21.2 (5.0)	17.2 (6.6)

Table 3 The mean ± s.e. mean serum theophylline levels in eight patients with chronic asthma for 6 h after three 250 mg doses of theophylline administered orally at 0, 2 and 4 h

	Time (hours)					
	1	*2*	*3*	*4*	*5*	*6*
Mean (s.e. mean) serum theophylline (μmol $litre^{-1}$)	23.9 (5.6)	37.2 (3.3)	55.6 (6.1)	63.3 (5.0)	97.8 (8.3)	97.8 (5.6)

The purpose of the salbutamol dose-response was to establish if possible the maximal degree of bronchodilator reversibility of airways obstruction attainable in these patients, in order to determine the relative potency of theophylline. However, it appeared that sixteen inhalations (1600 μg) of salbutamol may still have been submaximal. Other studies in patients with chronic, stable airways obstruction have shown a similar dose-response pattern to large doses of β-adrenoceptor agonist by inhalation (Svedmyr, Malmberg & Thiringer, 1972; Martin *et al.*, 1977; Marlin *et al.*, 1978). Shenfield & Paterson (1973) studied hospital patients with exacerbations of airways obstruction and showed more plateaued dose-response curves for bronchodilatation by β-adrenoceptor agonists, although the doses were not as high as in the present study. Patients with acute asthma may be less responsive to bronchodilators because factors such as mucosal oedema and mucus hypersecretion, which may lead to widespread mucus plugging of airways, will contribute to bronchoconstriction. These findings imply that in patients with chronic, stable asthma, when symptoms are poorly controlled with recommended doses of β-adrenoceptor agonists, judicious increases in size or frequency of dosage may produce further bronchodilatation and hence an improvement in symptoms. However, this situation may not apply to patients with acute, severe asthma, who for the reasons mentioned, may be less responsive to these drugs and will require intervention with other forms of treatment, e.g. corticosteroids.

When serum theophylline levels exceeded 55 μmol litre^{-1}, bronchodilatation was of a similar range to that achieved with both one (100 μg) and two (200 μg) inhalations of salbutamol. The mean peak theophylline response (5 h) was 41% of the mean peak salbutamol response (sixteen inhalations). Only one patient produced a better response with theophylline. Improvement in lung function with theophylline has been shown previously to vary directly with the logarithm of the plasma concentration, and to occur between 55 and 110 μmol litre^{-1}, with toxicity common above 110 μmol litre^{-1}, as seen in the present study (Jenne, Wyze, Rood & MacDonald, 1972; Mitenko & Ogilvie, 1973; Levy & Koysooko, 1975; Ogilvie, 1978; Weinberger, 1978). This work suggests that salbutamol by inhalation possesses a greater potential therapeutic range with a wider margin of safety than oral theophylline. The variability of theophylline clearance in man necessitates monitoring of plasma levels if the therapeutic range is to be achieved and toxicity avoided (Hendeles, Weinberger & Johnson, 1978).

G.E. MARLIN, M.R. HARRIS, J.A. KLUMPP & J. RUTLAND

Respiratory Unit, Concord Hospital, N.S.W., 2139, Australia

Received May 16, 1979

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