

# Intravenous salbutamol and aminophylline in asthma: a search for synergy

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**ABSTRACT** The bronchodilation produced by increasing intravenous doses of aminophylline, salbutamol, and a combination of aminophylline and salbutamol given in random order was determined in 10 stable asthmatics on three consecutive days. On a fourth day, response to placebo injections was determined. Forced expiratory volume in one second (FEV<sub>1</sub>) was measured at two-minute intervals after each dose until FEV<sub>1</sub> returned to a new baseline. At no dosage level was there synergy between the two agents in terms of either mean percentage increase in FEV<sub>1</sub> or the integrated response. The failure to demonstrate synergy has implications both with respect to the clinical use and the underlying mechanism of action of these drugs.

B<sub>2</sub> adrenergic stimulants and methyl xanthine derivatives are commonly prescribed together in the management of asthma. B<sub>2</sub> adrenergic stimulants increase production of cyclic (3,5) adenosine monophosphate (cyclic AMP) from ATP by stimulation of adenylyl cyclase.<sup>1</sup> Methyl xanthine derivatives reduce the rate of degradation of cyclic AMP by inhibition of phosphodiesterase.<sup>2</sup> Since B<sub>2</sub> adrenergic stimulants and methyl xanthine derivatives produce increases in cyclic AMP concentration by different mechanisms, the question arises whether the interaction between these two classes of drug is synergistic<sup>3</sup>—synergy being defined as an interaction between two agents when given in combination which produces a response greater than the sum of their individual responses.

Synergy has been demonstrated experimentally using guinea pig tracheal muscle, human leucocytes, and human lung fragments<sup>4-6</sup> but has not been demonstrated conclusively in vivo.<sup>7-9</sup> In an attempt to demonstrate synergy we have constructed dose-response curves to intravenous salbutamol and aminophylline when given separately and in combination.

## Methods

Ten well-controlled asthmatics requiring regular inhaled salbutamol and who showed greater than 15% improvement in forced expiratory volume (FEV<sub>1</sub>)

after inhalation of 200 µg salbutamol gave informed consent. Subjects recorded peak expiratory flow rate (PEFR) and an asthma score for two weeks before investigation to establish stability. The subjects were fasting and had received no bronchodilator therapy for at least eight hours before study.

On three consecutive mornings an intravenous cannula was inserted and FEV<sub>1</sub> values were recorded until consecutive values were identical. On three separate mornings salbutamol, aminophylline, or a combination of the two were given intravenously in random order, in increasing doses. The doses used were salbutamol 25, 50, 75, 100, 150, 200 µg; aminophylline 25, 50, 75, 100, 150, 200 mg; aminophylline + salbutamol 25, 25: 50, 50: 75, 75: 100, 100: 150, 150: 200, 200 mg/µg.

After each bolus, FEV<sub>1</sub> values were recorded every two minutes taking the best of two values until FEV<sub>1</sub> had returned to a stable baseline. The next bolus was then given. The maximum dose which could be given on any one day was determined by one of the following: the appearance of side-effects, the demonstration of no further increase in FEV<sub>1</sub>, or the limitation imposed by time taken at higher doses for the FEV<sub>1</sub> to return to a new baseline. On the fourth morning the response to placebo injections was recorded.

## Results

The mean pre-treatment values for FEV<sub>1</sub> on the four study days show no statistically significant difference.

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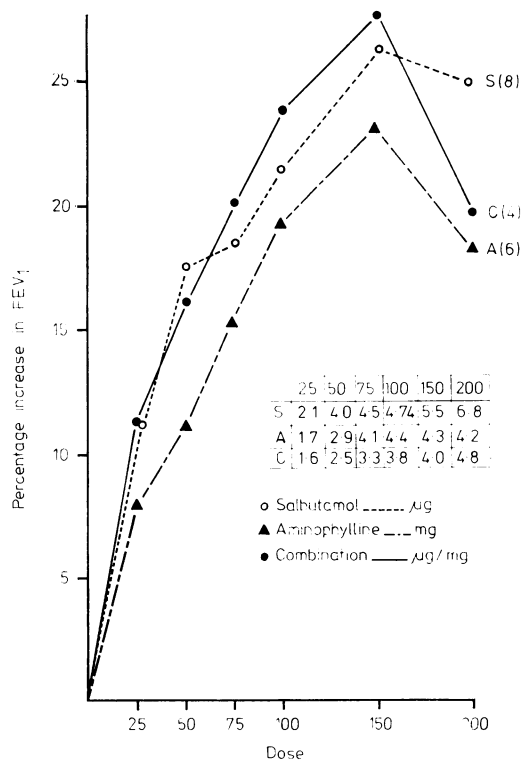


Fig 1 Mean percentage increase in  $FEV_1$  over daily baseline in 10 asthmatic patients (numbers in parentheses indicate number of patients who tolerated the 200  $\mu\text{g}/\text{mg}$  dose). The table indicates the standard errors.

The  $FEV_1$  responses produced by each injection were analysed in three different ways: increase in  $FEV_1$  from pre-treatment baseline to peak response was expressed as a percentage of the pre-treatment baseline—that is, percentage change in  $FEV_1$  over baseline. The mean values for percentage change in  $FEV_1$  are shown in fig 1 (the small table indicates the respective standard errors); no statistically significant response was seen to placebo injections. It can be seen that at 25 and 50  $\mu\text{g}$  doses of salbutamol the response is equivalent to salbutamol and aminophylline given in combination. However, at 75, 100, and 150  $\mu\text{g}/\text{mg}$  the responses caused by the combination were greater. Statistical analysis of these results with paired  $t$  testing and linear regression analysis showed a highly significant log dose response to all three drugs; however, the difference between salbutamol alone and the combination was not significantly different at these dosage levels.

Seven of the 10 patients showed a plateau in their dose-response curves at higher doses on all three treatment days, indicating that they were approaching their maximal response for that day. The im-

provement in  $FEV_1$  values for these patients was expressed as a percentage of the maximum improvement in  $FEV_1$  for that day. The mean responses are expressed in fig 2. Again, it can be seen that at 25 and 50  $\mu\text{g}/\text{mg}$  the increases resulting from the combination are equivalent to salbutamol when given alone. However, at 75 and 100  $\mu\text{g}/\text{mg}$  the responses resulting from the combination appear to be greater though the difference between the responses was not statistically significant.

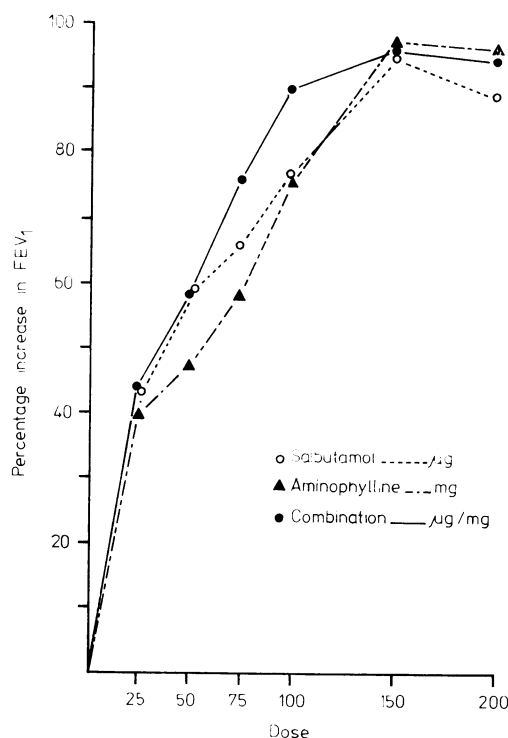


Fig 2 Mean percentage increase in  $FEV_1$  over maximum possible increase for seven patients who plateau between 100 and 200  $\mu\text{g}/\text{mg}$  for all three drugs. (Number in parentheses indicate number of patients who tolerated the 200  $\mu\text{g}/\text{mg}$  dose.)

Since the interaction between salbutamol and aminophylline may be related not to the peak response but to the area under the dose-response curve, a computer analysis of the areas under the curve for each dose of each drug was performed—integrated response (see appendix). The results (fig 3) show that there was a highly significant dose response in each case ( $p < 0.01$ ).

An individual comparison showed the combination to be significantly higher than aminophylline

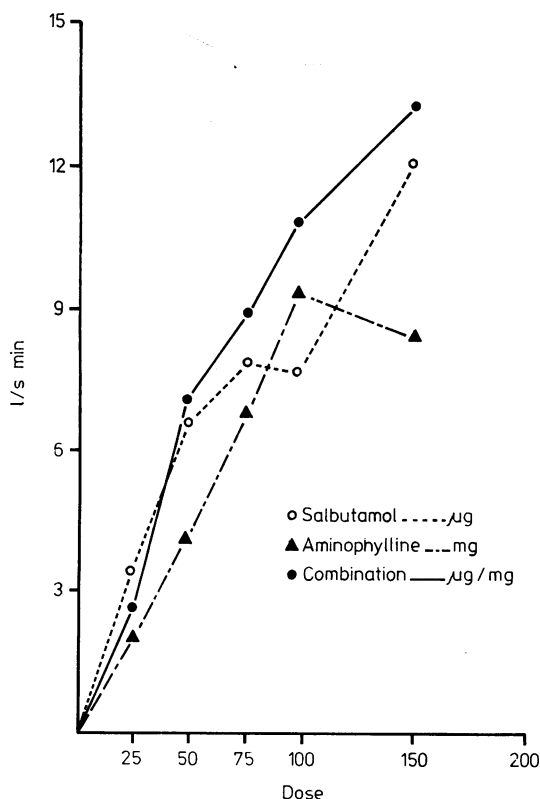


Fig 3 Mean integrated response for 10 asthmatic patients (see appendix).

alone ( $p < 0.05$ ). The linear regression lines for the three drugs were parallel and showed aminophylline to be lower than salbutamol, which was lower than the combination; however, the distance between the intercepts of the salbutamol and the combination dose-response regression lines was less than that between salbutamol and aminophylline, suggesting therefore that the response to aminophylline and salbutamol when given in combination is less than additive.

## Discussion

We have demonstrated a dose-response relationship to small intravenous doses of salbutamol and aminophylline, which is statistically highly significant with respect to  $FEV_1$  response and "integrated response". If synergy between these drugs had occurred then one would have expected the dose response curve of salbutamol combined with aminophylline to be above and to the left of the salbutamol curve depicted (fig 1)—for example, if 75 mg aminophylline produces a 15% improvement in  $FEV_1$  and 75  $\mu$ g

salbutamol produces an 18% improvement in  $FEV_1$ , then when the drugs are given in combination one would expect greater than 33% improvement in  $FEV_1$ . The observed response was 20%. Similarly, for all other doses used less than complete addition was seen when the drugs were given in combination.

The intravenous route was used in this study to avoid the variation in penetration associated with aerosol inhalation of bronchodilators. We have also avoided using different routes of administration since when an oral or intravenously administered drug produces a bronchodilator response, it will improve access of an inhaled drug so that any apparent interaction between the drugs may be caused partly by improved drug access rather than drug interaction.  $FEV_1$  was used to detect changes in lung function because of its simplicity, reproducibility, and its demonstration of clinically significant changes in airway obstruction. Failure to demonstrate synergistic interaction between aminophylline and salbutamol in terms of reversal of airways obstruction may be caused by the lability of the airways in asthmatics though we were careful to select stable asthmatics.

Methyl xanthine derivatives and B adrenergic stimulants have been shown to interact synergistically with respect to cyclic AMP levels in human lung fragments<sup>6</sup>; no such interaction has been shown in terms of improvement in  $FEV_1$ . A factorially designed study has shown synergistic interaction with respect to  $V_{max50}$ . This was statistically significant at 20 minutes only. In this study 250 mg aminophylline was administered intravenously at the same time as an inhalation of 0.16-0.18 mg of isoprenaline.<sup>7</sup> The same author was unable to demonstrate synergy between oral choline theophyllinate and salmetamol with respect to PEFR.<sup>9</sup> We have used standard dose-response curves to salbutamol, aminophylline, placebo, and salbutamol and aminophylline in combination and have shown highly significant increases in  $FEV_1$  and integrated response though we have been unable to show synergistic interaction. This calls into question the mechanism of action of B adrenergic stimulants and methyl xanthine derivatives.

It is proposed though not proven that B adrenergic stimulants and methyl xanthine derivatives produce bronchodilation by increasing cyclic AMP levels in bronchial smooth muscle. Increased levels of intracellular cyclic AMP stimulate calcium binding to the cell membrane and the sarcoplasmic reticulum, calcium concentration in the myoplasm is thereby reduced and muscle relaxation occurs.<sup>10</sup> It is suggested that the adrenaline-induced increase in calcium conductance in heart muscle results from an increase in the number of functional conductance channels.<sup>11</sup> There is also evidence suggesting that low

concentrations of B adrenergic agents may bypass adenylyl cyclase and directly stimulate calcium conductance.<sup>12</sup> A small pool of B receptors sufficient to initiate a maximal tissue response may not be coupled to adenylyl cyclase or if coupled to adenylyl cyclase the rise in cyclic AMP is too small to be measured. The remaining receptors or spare receptors may be responsible for most of the increase in cyclic AMP levels.<sup>13</sup> B adrenergic stimulants and phosphodiesterase inhibitors used in combination may produce a 27-fold increase in "free" cyclic AMP while bound cyclic AMP increases three to four fold indicating that after the initial increase in cyclic AMP little additional binding of cyclic AMP to receptors would be expected to occur.<sup>14</sup>

In view of this information, although B adrenergic stimulants and methyl xanthine derivatives might be expected to produce an additive or perhaps synergistic increase in cyclic AMP, we would not expect synergism with respect to bronchial smooth muscle relaxation. In this study the response to intravenous salbutamol and aminophylline when given in combination with respect to peak FEV<sub>1</sub> response and integrated response was less than would have been expected from the response when these drugs were given separately. Although we have demonstrated a small degree of addition, there was no evidence of synergy.

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## Appendix

The areas were measured by a trapezoidal rule. Given that the FEV<sub>1</sub> denoted by  $x_1, x_2 \dots x_n$  are measured at  $t_1, t_2 \dots t_n$  and the base line is  $x_b$  the area is calculated by:

$$\text{Area} = \frac{1}{2} \sum_{i=1}^n \left( (x_i - x_b) + (x_{i-1} - x_b) \right) (t_i - t_{i-1})$$

FEV<sub>1</sub> was measured in litres/s and time in minutes so that the area has units, (litres/s). minutes. The areas were calculated for each dose of each drug over 30 minutes. Results extending beyond 30 minutes were ignored. If measurements were stopped before 30 minutes, FEV<sub>1</sub> was assumed fixed from the last measurement to the end of the period and the area of this additional rectangle was recorded separately. The mean response and the variance of the response were plotted against dose. The variances increased roughly in proportion to the means. A linear regression analysis of log response against dose was conducted. The placebo dose and the 2000  $\mu\text{g}/\text{mg}$  dose were excluded.