Cumulative dose-response curves for assessing combined effects of salbutamol and ipratropium bromide in chronic asthma

B.M. Grandordy*, V. Thomas*, D. de Lauture**, J. Marsac*

ABSTRACT: We investigated whether salbutamol (S) and ipratropium bromide (IB) exerted a true additive bronchodilator effect in asthma. In fifteen selected chronic asthmatics, individual cumulative dose-response curves to S and IB were performed on two separate days (linear regression of bronchodilator response (ΔFEV₁) between 20 and 80% of maximal response, versus log dose), and the dose of S equipotent to the IB dose giving the maximal bronchodilator effect (IBₜₐₐₜ) was calculated by interpolation of each S curve. On two other days, each patient received IBₜₐₐₜ or the equipotent S dose followed by an additional 400 µg S. On day 1 or 2, FEV₁ reached 220±410 ml and 2410±380 ml (p<0.05) after the maximal dose of IB and S respectively. On day 3 or 4 after pretreatment by IB or S an additional 400 µg S gave a further increase, which was similar in both series (315 and 320 ml, respectively). FEV₁ after combination treatment reached 238±350 ml and was not significantly different from the maximal effect of S (2440±290 ml). We conclude that S and IB exert a true pharmacological additive effect, since the combination effect is as great as the maximal effect of the most potent drug (S) and greater than the maximal effect of IB, and that the same additional dose of S gives the same increase after equipotent doses of S and IB.

In numerous short-term studies of the bronchodilator effect of combinations of beta-agonists and anticholinergics [1–8] a single dose of each drug is used, without previous evaluation of the maximal effect or equipotent doses of the two bronchodilators [9].

Combined bronchodilator therapy [10, 11] may be of some benefit when the second drug causes further bronchodilatation after maximal effect of the first. Thus, it has been shown in chronic bronchitic patients that salbutamol (S) causes a further improvement of forced expiratory volume in one second (FEV₁) after maximal effect of theophylline [12]. In acute asthma, improvement follows inhalation of ipratropium bromide (IB) after a maximal dose of S [4, 5]. In chronic asthma, the effect of S after a high dose of IB has seldom been studied [13]. Our aim was to determine whether there was an interactive bronchodilator response between salbutamol and ipratropium bromide. In fifteen stable asthmatic patients we assessed, from cumulative dose-response curves to S and IB, the IB dose (IBₜₐₐₜ) after which no significant further FEV₁ improvement was observed. We also assessed the dose of S equipotent to IBₜₐₐₜ. In the second part of our study, the effect of an additional S dose following IBₜₐₐₜ or the equipotent S dose was studied.

Patients and methods

Patients

Fifteen patients meeting American Thoracic Society (ATS) criteria for asthma [14] entered the study (table 1); all had severe perennial asthma with chronic airway obstruction for three months or more. Reversibility of airway obstruction to beta-agonists, evaluated on several occasions, was good: forced expiratory volume in one second (FEV₁) increased by >35% above baseline on 1 mg inhaled salbutamol, on at least one occasion in the preceding three months, and in six patients (nos 1, 2, 5–7 and 9) normal values were then reached. Other causes of chronic airway obstruction (such as smoking, professional exposure to respiratory hazards, cystic fibrosis or bronchial dystrophy) had not been identified. The patients were all in a stable state: unchanged daily medication, no increase in exertional

Keywords: Additive effect; anticholinergics; beta-agonists; dose-response curves, equipotent doses; selection of patients.

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The occurrence of IB peak since the 
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20 μg 
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30 μg 
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the optimal 
of IB (IBopt).

When IB was given in a cumulative way, FEV₁ after 80 μg was not significantly different from FEV₁ after higher doses (120, 160, and 200 μg). We therefore evaluated the time-course of the IB dose after which no significant further FEV₁ improvement was observed (IBopt). The first seven patients were asked to attend the clinic for a supplementary day on which they were given IB in a manner similar to that used for the dose-response curve. Since we found consistent results in the occurrence of IBopt peak effect (<30 min), and since the supplementary day substantially increased inconvenience due to the protocol for the patients, this procedure was then discontinued. The occurrence of IBopt peak effect less than 30 min after administration showed that, under the conditions of the cumulative concentration-response curve, the effect of a given IB dose cannot be due to the residual effect of the previous dose.

On days 3 and 4, the effects of additional 400 μg S (Sopt), after pre-treatment with IBopt or the equipotent dose of S (S₅₀) were compared; both pre-treatments were administered as dose-response curves on day 1 or 2, and IB was administered 30 min after IBopt or the equipotent dose of S.

On days 3 and 4, FEV₁ was also measured at 30 min intervals for 2.5 h after the last drug inhalation.

Experimental details

Before each study day, bronchodilator drugs were withheld for 12 h, and long-acting theophyllines for 24 h. Steroids and disodium cromoglycate, when prescribed, were not discontinued. All tests began at 9 a.m. Drug inhalation was carefully supervised: puffs were given at the beginning of a slow full inspiration, at the end of which the patients held their breath for 4 s. FEV₁ (best of three recordings) was measured with a wet spirometer (Gauthier, model Cara, France). Predicted values for FEV₁ were those of the European Community for Coal and Steel (European Society for Clinical Respiratory Physiology) [16].

Statistical analysis

Data were analysed by analysis of variance (ANOVA) and Student's t-test for paired data, at a significance level of p<0.05. In this way, each subject served as his or her own control. S and IB dose-response curves were analysed by linear regression of all points between 0 and 80% of maximal response obtained for each

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Th: theophylline; B₂₂: β₂₂-agonist; D: disodium cromoglycate; A: anticholinergic; C: oral steroid; IC: inhaled steroid.

dyspnoea or nocturnal asthma, no consistent change in b.i.d. measurements of peak expiratory flow rate in the preceding month.

Experimental design

The fifteen patients were studied on four days within a three-week period.

On days 1 or 2, according to randomization, cumulative dose-response curves to S were performed as previously described [15]: two doses of 100 μg or 20 μg (S or IB, respectively) followed by four doses of 200 μg or 40 μg (S or IB) were inhaled at 30 min intervals (6 data points). Metered-dose inhalers were used to deliver both drugs. FEV₁ was the measured variable. Dose-response curves were calculated by linear regression of the bronchodilator response (ΔFEV₁) between 20 and 80% of maximal response, versus log dose. By interpolation of individual cumulative dose-response curves to S, we assessed the dose of S which gave the same increase in FEV₁ as the optimal dose of IB (IBopt).

Table 1. - Clinical data and baseline spirometric data in 15 asthmatics
Results

Initial basal FEV₁ ranged from 31 to 70% predicted, and for each patient was not significantly different by ANOVA on any of the study days (table 1). FEV₁ was not significantly different after 600 µg S or higher S doses, nor after 80 µg IB or higher IB doses. Thus, dose-response curves apparently plateaued after mean values of 600 µg S and 80 µg IB.

The calculated dose-response curve to S and IB between 20 and 80% of the maximal response was log-linear for each patient (0.92<cr<0.99) (fig.1). After maximal cumulative doses, on day 1 or 2, maximal cumulative dose-response curves appeared to plateau between 400, 600, 800 µg, and for each patient was not significantly different by ANOVA on any of the study days (table 1). The combined effects of S and IB are shown in figure 3 (individual data) and figure 4 (mean for all fifteen patients). IBₘₐₓ or the equipotent dose of S administered on days 3 and 4 gave a similar FEV₁ increase, which did not differ from that observed on days 1 or 2 (2060±320 ml after IBₘₐₓ and 2000±290 ml after the equipotent dose of S (paired t-test, NS). FEV₁ rose further to 2380±350 ml and 2440±290 ml (NS). These latter values were not significantly different

Normal FEV₁ values (ml) were significantly different: 2410±380 ml on S and 2200±410 ml on IB (p<0.05).

In five of the fifteen patients (nos 6, 7 and 13-15) the highest FEV₁ on IB was within 15% of that on S. The S dose equivalent to IBₘₐₓ, calculated by interpolation of the S dose-response curve, was 200 to 300 µg in 11 patients, 100 µg, and 400 µg each in two patients respectively (fig.1).

In all of the seven patients who called on a supplementary day, no FEV₁ increase was observed more than 30 min after the last IB inhalation (fig.2). The combined effects of S and IB are shown in

![Graphs showing dose-response curves for S and IB](image-url)
from FEV\textsubscript{1} after the maximal dose of S on day 1 or 2, but were significantly greater than the value after the maximal IB dose on day 1 or 2 (p<0.01).

\[ \Delta \text{FEV}_1 \]

![Fig. 4. Mean FEV\textsubscript{1} increase after IB, or the equipotent dose of salbutamol (open boxes), and mean FEV\textsubscript{1} increase due to 400 \textmu g salbutamol (hatched boxes) after both pretreatments in 15 asthmatics (mean values of the individual data of table 1).]

Discussion

The cumulative dose-response curve to each drug in patients allowed the calculation of the IB dose giving maximal bronchodilatation to this drug, and of the S dose giving the same bronchodilator response as a pre-selected dose of IB.

Cumulative inhalation of IB or S gave reproducible results. Recently Britton and Tattersfield [17], showed that airway response to inhaled isoprenaline may be greater with a cumulative than a non-cumulative inhalation technique. However, both techniques give reproducible results, and the authors concluded that neither of the two techniques can be invalidated in view of their results, but that they must not be compared directly. The greater airway response with the cumulative technique may be due to the fact that the bronchodilatation produced by the first dose allows a second dose to reach peripheral bronchi, which the first dose cannot reach. However, some data have shown that bronchodilator drugs like atropine [18, 19] and beta-agonists [20] act on small and large airways after a single, inhalation, demonstrating that first puffs may also reach peripheral bronchi.

The peak effect of the IB dose giving maximal bronchodilatation was obtained within 30 min after inhalation of the complete dose, in agreement with some reports [18, 21] but in contrast to others [22]. Thus, for both drugs the peak effect of each dose seems to occur before the administration of the following dose. Similarly, on days 3 or 4, further dilatation caused by an additional 400 \textmu g of S after a priming dose of IB is due to S itself and not to the delayed effects of IB. Our patients behaved like "responders" to anticholinergics. They had chronic asthma, diagnosed on a history of nocturnal wheezing attacks with normal function in-between, absence of other known causes of chronic obstructive lung disease and magnitude of the bronchial response to salbutamol (0.6 < FEV\textsubscript{1} < 1.4 l in the present study). At the time of the study, their asthma had evolved to chronic airway obstruction (initial FEV\textsubscript{1} between 31 and 70% predicted).

It has already been reported [1-8, 13] that a dose of S, selected at random, produces further FEV\textsubscript{1} increase after a dose of IB, selected in the same manner, (or IB after S). We compared the combined effect of S and IB to the maximal effect of each drug. In combined inhalations, IB was administered first, because it was the less potent of the two bronchodilators, and thus it was more space to dilate after its maximal effect, allowing measurement of the effect of the second drug to be more accurate. Furthermore, it is generally agreed that the order of administration of both drugs (IB before S, or S before IB) does not influence the magnitude of the bronchodilator response [13], although a recent study suggests that duration of action but not peak effect is greater when an anticholinergic is administered first [6].

In two recent studies the effect of combined maximal doses of S and IB has been studied in acute asthma [4, 5]. In one study only, S was administered in a cumulative way, before inhalation of IB [4]; however, although IB gave a further rise in FEV\textsubscript{1}, after peak-effect of S, no comparison of the combined effect of S and IB with the maximal effect of each drug was provided. In the other study [5], a purported maximal dose was administered, but there was no evaluation of the degree of bronchodilatation actually achieved in the patients. Handslip et al. [23] demonstrated no synergistic and little additive effect of the combination of increasing doses of salbutamol and aminophylline up to maximal bronchodilator doses of each drug.

We found that maximal FEV\textsubscript{1} increase is smaller on IB than on S. Equi-dose doses, i.e. doses giving the same bronchodilatation, could be calculated in all patients. According to the recommendations of Svärdmyr [24] we evaluated the effect of the same additional S dose after equipotent doses of S and IB. This additional S caused a similar increase in FEV\textsubscript{1}, so that FEV\textsubscript{1} after both combinations did not differ, neither did they differ from FEV\textsubscript{1} after maximal S dose but were significantly higher than the maximal FEV\textsubscript{1} after IB. In addition, further increase due to S was observed even in patients (nos 2, 5, 9-11, 14 and 15) in whom 80 \textmu g IB had already brought FEV\textsubscript{1} to within 15% of its value after 200 \textmu g of the drug.

We conclude that there is a true pharmacological interaction between S and IB, since the combination of both drugs gives a greater effect than the maximal dose of IB. However, we found no potentiation or synergistic effect between both drugs since 1) their combined effect is similar to the maximal effect of S.
even though predicted FEV<sub>1</sub> is not reached; 2) the same additional S dose gives the same bronchodilator effect after equipotent doses of IB and S. The additive effect between S and IB would make it possible to obtain optimal bronchodilator effects in patients in whom side-effects to either drugs are liable to occur or to optimize bronchodilatation in patients treated on a long-term basis.

Acknowledgements: We are grateful to A. Lockhart for helpful comments on the manuscript.

References


RÉSUMÉ: Nous avons recherché si le salbutamol (S) et le bromure d'ipratropium (IB) exerçaient un véritable effet additif bronchodilatatateur dans l'asthme. Chez 15 asthmatiques sélectionnés, des courbes dose-réponse cumulatives individuelles ont été réalisées pour S et IB, à des jours différents (régression linéaire de la réponse bronchodilatatrice (ΔFEV<sub>1</sub>) entre 20 et 80% de la réponse maximale, par rapport au logarithme de la dose). La dose de S donnant un effet semblable à la dose de IB d'une utilisation si l'effet bronchodilatateur maximal (IB<sub>max</sub>) a été calculé par interpolation sur la courbe dose-réponse à S. Lors de deux autres épreuves, chaque patient a reçu IB<sub>max</sub> ou la dose équivalente de S, suivies par 400 μg de S supplémentaires. Le 1er et le 2<sup>ème</sup> jour, le VEMS a atteint 2200±410 ml et 2410±380 ml (p<0.05) respectivement. Le 3<sup>ème</sup> et le 4<sup>ème</sup> jour, 400 μg S a donné un accroissement supplémentaire du VEMS après le traitement par IB ou S, et cet accroissement était semblable dans les deux cas (315 et 320 ml respectivement). Le VEMS après le traitement combiné a atteint 2380±350 ml, une valeur comparable à l'effet maximal de S (2440±290 ml). Nous concluons que S et IB exercent un véritable effet additif pharmacologique puisque la combinaison donne un effet aussi important que le plus puissant des deux bronchodilatatateurs (S) et plus grand que l'effet maximal de IB, et aussi que la même dose supplémentaire de S donne la même augmentation de VEMS après deux doses équivalentes de S et de IB.