Eur Resp J
1988, 1, 531–535

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

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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 (ΔFEV_1) 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 (IB_{opt}) was calculated by interpolation of each S curve. On two other days, each patient received IB_{opt} or the equipotent S dose followed by an additional 400 μg S. On day 1 or 2, FEV_1 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). FEV_1 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.

Eur Respir J., 1988, 1, 531–535

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Keywords: Additive effect; anticholinergics; $beta_2$-agonists; dose-response curves, equipotent doses; selection of patients.

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 (FEV_1) 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 (IB_{opt}) after which no significant further FEV_1 improvement was observed. We also assessed the dose of S equipotent to IB_{opt}. In the second part of our study, the effect of an additional S dose following IB_{opt} 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 $beta_2$-agonists, evaluated on several occasions, was good: forced expiratory volume in one second (FEV_1) 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

Table 1. – Clinical data and baseline spirometric data in 15 asthmatics

Patient no.	Age/Sex yrs	Height m	Asthma duration yrs	Atopy	Current medication			FEV_1 ml pred	FEV_1 ml S_{eq}	FEV_1 ml IB_{opt}	FEV_1 ml $IB_{opt}+_{ad}$	FEV_1 $S_{ad}+S_{ad}$
1	35 M	1.59	10	+	Th	$ß_2$		3020	1500	1390	1420	1290
2	43 F	1.65	11	-	Th	$ß_2$		2510	1510	1390	1450	1500
3	25 F	1.69	3	+	Th	D		3070	2200	2300	2150	2050
4	40 F	1.55	15	-	Th	$ß_2$	C	2230	1300	1250	1320	1200
5	45 M	1.70	5	-	$ß_2$	A	IC	3220	1290	1120	1050	1250
6	35 M	1.79	12	+	$ß_2$	IC		3900	1760	1950	1820	1930
7	25 F	1.53	10	+	Th	$ß_2$	IC	2440	1420	1530	1400	1600
8	40 M	1.68	16	+	$ß_2$	IC	C	3230	1340	1450	1330	1500
9	44 F	1.65	7	+	Th	$ß_2$	IC	2510	1070	1120	1080	1200
10	55 M	1.74	15	-	$ß_2$	IC		2930	1640	1710	1610	1680
11	32 M	1.82	7	+	Th	$ß_2$	C	4230	2180	2280	2340	2100
12	53 F	1.68	24	+	Th	$ß_2$	IC	2900	1210	1300	1390	1400
13	65 M	1.65	20	-	Th	A	IC	2340	1290	1320	1350	1440
14	50 M	1.71	5	-	Th	$ß_2$	C	3050	960	990	1070	1120
15	48 F	1.66	10	-	Th	IC		2500	1620	1700	1540	1490

Th: theophylline; $ß_2$: $ß_2$-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. FEV_1 was the measured variable. Dose-response curves were calculated by linear regression of the bronchodilator response (ΔFEV_1) 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 FEV_1 as the optimal dose of IB (IB_{opt}).

When IB was given in a cumulative way, FEV_1 after 80 µg was not significantly different from FEV_1 after higher doses (120, 160, and 200 µg). We therefore evaluated the time-course of the IB dose after which no significant further FEV_1 improvement was observed (IB_{opt}). 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 IB_{opt} 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 IB_{opt} 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 (S_{ad}), after pre-treatment with IB_{opt} or the equipotent dose of S (S_{eq}) were compared; both pre-treatments were administered as for dose-response curves on day 1 or 2, and S_{ad} was administered 30 min after IB_{opt} or the equipotent dose of S.

On days 3 and 4, FEV_1 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 witheld 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. FEV_1 (best of three recordings) was measured with a wet spirometer (Gauthier, model Cara, France). Predicted values for FEV_1 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 20 and 80% of the maximal response obtained for each

patient (plot of FEV_1 variation *versus* the logarithm of the inhaled S dose).

Results

Initial basal FEV_1 ranged from 31 to 70% predicted, and for each patient was not significantly different by ANOVA on any of the study days (table 1).

FEV_1 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 ($0.92<r<0.99$) (fig.1).

After maximal cumulative doses, on day 1 or 2, maximal FEV_1 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 FEV_1 on IB was within 15% of that on S. The S dose equipotent to IB_{opt}, 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).

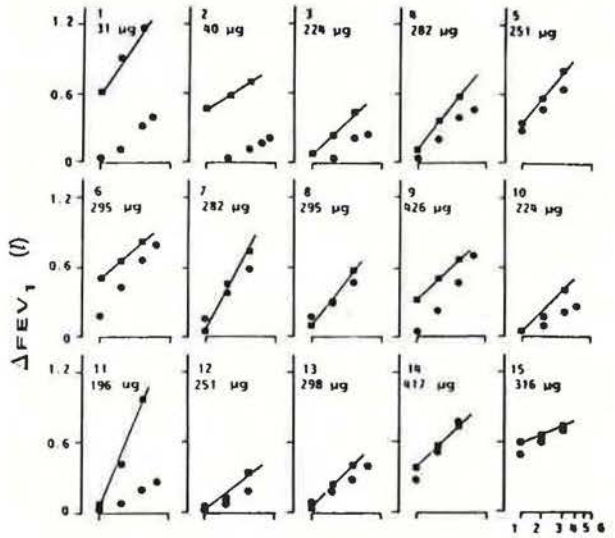

Fig. 1. – Individual cumulative dose-response curves to salbutamol (; solid line) expressed as a linear regression of ΔFEV_1 *versus* log (salbutamol dose), for FEV_1 responses between 20 and 80% of the maximal response in 15 chronic asthmatic patients. Responses to ipratropium bromide (●) have been expressed in the same way, but the regression line has not been drawn. For each patient, the dose of S equipotent to maximal IB (highest IB point on the y-axis) has been calculated by interpolation of the dose-response curve to salbutamol, and the calculated value is indicated for each patient. The numbers indicated on the x-axis (1–6) denote salbutamol and ipratropium cumulative doses (100, 200, 400, 600, 800 and 1000 μg; and 20, 40, 80, 120, 160, and 200 μg, respectively). Because linear regression has been calculated between 20 and 80% of the maximal FEV_1 response, some of the data points have not been taken into account for the calculation of the regression line, and curves represent the linear regression of 3–5 points.

In all of the seven patients who called on a supplementary day, no FEV_1 increase was observed more than 30 min after the last IB inhalation (fig. 2).

The combined effects of S and IB are shown in figure 3 (individual data) and figure 4 (mean for all fifteen patients). IB_{opt} or the equipotent dose of S administered on days 3 and 4 gave a similar FEV_1 increase, which did not differ from that observed on days 1 or 2 (2060±320 ml after IB_{opt} and 2090±290 ml after the equipotent dose of S (paired t-test, NS). FEV_1 rose further to 2380±350 ml and 2440±290 ml (NS). These latter values were not significantly different

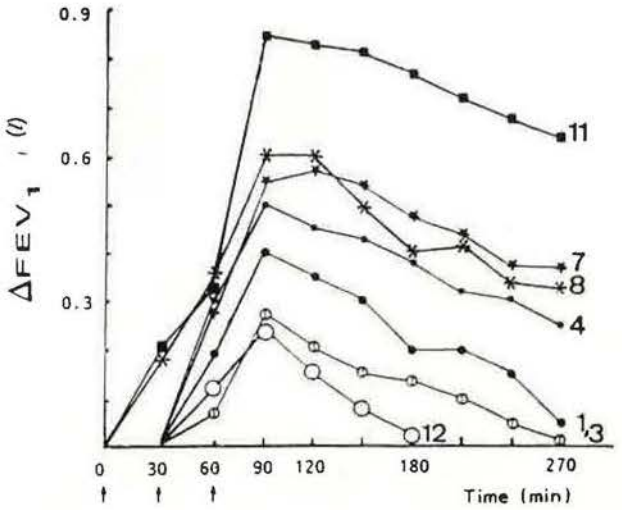

Fig. 2. – Time-course of the FEV_1 response to ipratropium (IB_{opt}) in 7 patients (nos 1, 3, 4, 7, 8, 11, 12) (see text). IB_{opt} was administered in the same manner as for cumulative dose-response curve: 2x20 μg followed by 40 μg of the drug (arrows). Maximal improvement of FEV_1 is observed within 30 min of the last inhalation: Then FEV_1 starts to decrease.

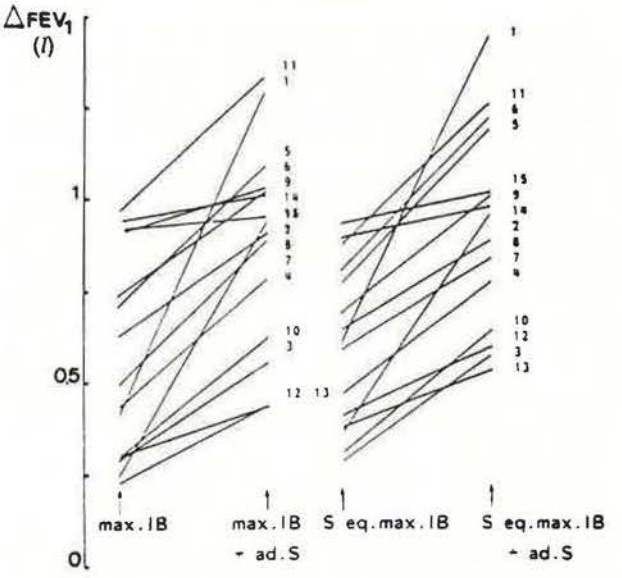

Fig. 3. – Individual bronchodilator effect of IB_{opt} (80 μg for all patients, except nos 6, 9 and 13 who received 120 μg) or the equipotent dose of salbutamol (S), and further FEV_1 increase due to 400 μg additional salbutamol (S_{ad}) after both pre-treatments.

from FEV_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 ($p<0.01$).

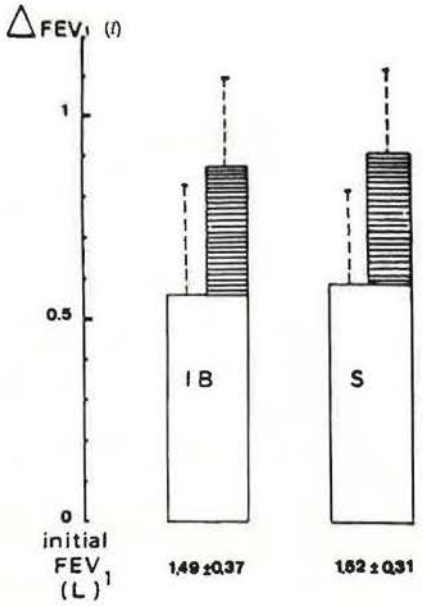

Fig. 4. – Mean FEV_1 increase after IB_{eqt} or the equipotent dose of salbutamol (open boxes), and mean FEV_1 increase due to 400 μg salbutamol (hatched boxes) after both pre-treatments in 15 asthmatics (mean values of the individual data of table 1).

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 μg 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 ($0.6\ l < FEV_1 < 1.4\ l$ in the present study). At the time of the study, their asthma had evolved to chronic airway obstruction (initial FEV_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_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 there 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_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_1 increase is smaller on IB than on S. Equipotent doses, *i.e.* doses giving the same bronchodilatation, could be calculated in all patients. According to the recommendations of SVEDMYR [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_1 so that FEV_1 after both combinations did not differ, neither did they differ from FEV_1 after maximal S dose but were significantly higher than the maximal FEV_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 μg IB had already brought FEV_1 to within 15% of that after 200 μg 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_1 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.

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RÉSUMÉ: Nous avons recherché si le salbutamol (S) et le bromure d'ipratropium (IB) exerçaient un véritable effet additif bronchodilatateur 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_1) 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 produisant un effet bronchodilatateur maximal (IB_{opt}) a été calculée par interpolation sur la courbe dose-réponse à S. Lors de deux autres épreuves, chaque patient a reçu IB_{opt} ou la dose équivalente de S, suivies par 400 µg de S supplémentaires. Le 1er et le 2eme jour, le VEMS a atteint 2200±410 ml et 2410±380 ml ($p<0.05$) respectivement. Le 3eme et le 4eme jour, 400 µg S a donné un accroissement supplémentaire du VEMS après le prétraitement 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 bronchodilatateurs (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.