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Optimal dose of salbutamol respiratory solution: comparison of three doses with plasma levels

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ABSTRACT Salbutamol solution is usually administered by nebuliser in a dose of 5 mg. Little evidence exists that this is the optimal dose for bronchodilatation or that this dose is without side-effects. Twelve patients with asthma were given increasing doses of salbutamol, 1·5 mg, 3·0 mg, 7·5 mg, and placebo. Treatments were administered twice daily for four days in a double-blind manner. Measurements of ventilatory capacity, pulse rate, and tremor were recorded before and for three hours after treatment. There was a significant dose-related response for FEV1 and peak flow rate. There was also a significant dose-related response in pulse rate and tremor. The incidence of palpitations was similarly related to dose. Plasma levels of salbutamol were measured before and after treatment with salbutamol and showed a dose related increase in salbutamol absorption which begins to be evident after the 3·0 mg dose. Three milligrams of salbutamol nebuliser solution may be an optimal dose, producing satisfactory bronchodilatation but fewer side-effects related to systemic absorption.

Adequate bronchodilatation with minimal systemic side-effects can be achieved with 100 μg of aerosolised salbutamol in patients with mild or moderate airways obstruction caused by asthma.[1] For cases with severe asthma, salbutamol respirator solution is commonly prescribed using various delivery techiques.

Previous studies of salbutamol respirator solution have shown adequate bronchodilatation using 10 mg[2] and 5 mg.[3] These doses may be associated with systemic side effects of tremor and palpitations. To clarify the optimal dose of salbutamol respirator solution without associated side-effects, three doses were compared and correlated to the plasma levels of salbutamol.

Methods

Twelve patients (seven men, five women; mean age 56 years, range 24 to 67 yr) were studied. All had been admitted to hospital with persistent uncontrolled wheezing and a peak expiratory flow rate (PEFR) of less than 50% of predicted normal. Most were receiving concurrent oral or inhaled corticosteroids and this dose was not altered during the study. No bronchodilator drugs were administered for 12 hours before study.

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Four treatment regimens were compared using a modified Latin Square distribution. The regimens were (1) placebo, (2) salbutamol 1·5 mg in 3 ml solution, (3) salbutamol 3·0 mg in 3 ml solution, and (4) salbutamol 7·5 mg in 3 ml solution.

These were administered double-blind over a study period of four days, two treatments being given each day at 0900 and 1400 hours respectively. Each treatment was given once in the morning and once in the afternoon. Drugs were administered via a Hudson disposable nebuliser over 15 minutes.

Measurements of forced expiratory volume in one second (FEV_1) and PEFR were recorded from a McDermott digital spirometer and Wright's meter respectively at 30 minutes and 15 minutes before inhalation, at 15 minute intervals for one hour after therapy, and half-hourly for a further two hours. At each point the best of three technically satisfactory measurements was recorded. Pulse rate over a full minute was recorded every five minutes for the half hour before treatment and after treatment before each set of ventilatory measurements.

Measurements were curtailed where after therapy a patient was symptomatic at 30 minutes. Salbutamol respirator solution (5 mg) was then given and the data analysed to that point. Table 1 shows the number of patients in each group requiring this dose of salbutamol.

Before each recording of ventilatory function the presence of hand tremor was noted and the patient

Table 1 *Patients taking extra salbutamol after treatment*

Treatment	*Morning*	*Afternoon*
Placebo	4	7
Salbutamol 1·5 mg/3 ml	0	1
Salbutamol 3 mg/3 ml	1	0
Salbutamol 7·5 mg/3 ml	0	1

asked about the presence of palpitations.

Non-parametric statistical methods were used for the pulse rate and ventilatory data because they were not normally distributed.

Two measures of ventilatory function were calculated for each dose regimen, namely the peak change in FEV_1 and PEFR from baseline and the average change in FEV_1 and PEFR determined by trapezoidal integration of the areas under the response time curves.

On two of the four study days 10 ml of venous blood was taken from each patient just before and 30 minutes after the 0900 treatment. The blood was placed in heparinised tubes and immediately spun down, the plasma separated and frozen at −20°C. Plasma salbutamol was later extracted and the concentration measured.[4]

Results

BASELINE VALUES

Two baselines were determined on each day, once before 0900 hours and once before 1400 hours for pulse, FEV_1 and PEFR by summing the values obtained over the previous 30 minutes and obtaining the mean. The overall mean morning baseline for FEV_1 was 1·45 l and in the afternoon 1·55 l. For PEFR the mean morning baseline was 260 l/s and that in the afternoon 280 l/s.

For both morning and afternoon the baselines were classified into four groups according to treatment. There was no significant difference between them at either time. However, for each treatment group the baseline at 1400 hours was significantly greater than at 0900 hours ($p < 0·05$ by Wilcoxon's signed rank test), but these differences in baselines did not depend on which treatment had been given in the morning, being the same for placebo as any of the salbutamol doses. Thus, there did not seem to have been a carry-over effect for any morning treatment.

THERAPEUTIC RESPONSES

There was a significant dose-related response for the variables (peak value—baseline) and average response for both PEFR and FEV_1 in both morning and afternoon studies ($p < 0·01$ by Pages' test).[5]

Table 2 shows the median values and ranges for (peak value—baseline) expressed as a percentage of baseline for FEV_1 and Table 3 shows the same for PEFR. Tables 4 and 5 give the median values and ranges for average response for FEV_1 and PEFR respectively.

Table 2 $\left(\frac{\textit{Peak value—baseline}}{\textit{Baseline}}\right) \times 100$ *for* FEV_1

		Treatment			
		Placebo	*Salbutamol*		
			1·5 mg/ 3 ml	*3·0 mg/ 3 ml*	*7·5 mg/ 3 ml*
Morning	Median	13	24	25	34
	Range	−3, 72	10, 91	0, 157	0, 94
Afternoon	Median	3	15	17	26
	Range	−13, 28	−2, 91	5, 91	8, 60

Table 3 $\left(\frac{\textit{Peak value—baseline}}{\textit{Baseline}}\right) \times 100$ *for PEFR*

		Treatment			
		Placebo	*Salbutamol*		
			1·5 mg/ 3 ml	*3·0 mg/ 3 ml*	*7·5 mg/ 3 ml*
Morning	Median	16	26	24	32
	Range	−5, 52	9, 72	15, 171	1, 82
Afternoon	Median	2	12	20	30
	Range	−19, 17	5, 90	5, 35	8, 55

Table 4 *Average response for* FEV_1

		Treatment			
		Placebo	*Salbutamol*		
			1·5 mg/ 3 ml	*3·0 mg/ 3 ml*	*7·5 mg/ 3 ml*
Morning	Median	0·06	0·18	0·22	0·33
	Range	−0·03 0·48	0·06, 0·99	−0·10, 0·74	−0·04, 1·13
After-noon	Median	−0·03	0·05	0·11	0·23
	Range	−0·29, 0·30	−0·01, 1·09	0·03, 1·10	0·09, 0·95

Table 5 *Average response for PEFR*

		Treatment			
		Placebo	*Salbutamol*		
			1·5 mg/ 3 ml	*3·0 mg/ 3 ml*	*7·5 mg/ 3 ml*
Morning	Median	5	30	40	65
	Range	−10, 80	−5, 130	15, 200	−15, 150
After-noon	Median	−5	25	15	50
	Range	−60, 10	−25, 150	−10, 150	5, 115

Wilcoxon's rank sign sum test showed the 1·5 mg dose responses to be significantly different from placebo for all measurements except for average response for PEFR in the morning ($p < 0·05$ for the morning and $< 0·01$ for the afternoon). For average response in terms of PEFR the 3 mg dose was significantly different from placebo ($p < 0·02$).

SIDE-EFFECTS

Table 6 shows the median value with ranges for peak changes in pulse rate after each dose expressed as a percentage of baseline and table 7 gives the same for average response. For both the morning and afternoon there was a significant dose-related response for both peak changes and average responses ($p < 0·01$ by Pages' test).

Table 6 $\left(\frac{\textit{Peak value—baseline}}{\textit{Baseline}}\right) \times 100$ *for pulse*

		Treatment							
		Placebo	*Salbutamol*						
			1·5 mg/ 3 ml		*3·0 mg/ 3 ml*		*7·5 mg/ 3 ml*		
Morning	Median	5		6		7		14	
	Range	−1,	13	0,	23	1	53	5,	51
After-noon	Median	6		7		9		15	
	Range	−4,	21	−2,	26	1,	50	2,	55

Table 7 *Average response for pulse*

		Treatment							
		Placebo	*Salbutamol*						
			1·5 mg/ 3 ml		*3·0 mg/ 3 ml*		*7·5 mg 3 ml*		
Morning	Median	−4		−3		−2		5	
	Range	−14,	3	−13,	8	−10,	9	−6,	13
After-noon	Median	1		−1		−1		3	
	Range	−5,	5	−9,	9	−5,	11	−1,	14

Only the changes in pulse rate for the 7·5 mg dose are consistently significantly different from placebo for both peak changes and average response ($p < 0·02$). The 3·0 mg dose changes were significantly different from placebo only in the morning for the peak change ($p < 0·05$).

Tremor occurred in two patients after placebo and 1·5 mg, six after 3 mg and nine after 7·5 mg. These data were tested by a linear logistic model to assess whether the slope of effect against dose was significantly different from zero. This showed a significant dose related response ($p < 0·01$). Taking the placebo effect into account the incidence of tremor after the 7·5 mg dose was twice that at 3·0 mg. The numbers of patients complaining of palpitations were too small for adequate statistical analysis.

BLOOD LEVELS

Table 8 shows the changes in plasma levels of salbutamol after each dose tested. The distribution of sampling was predetermined although blind to the investigators and corresponds to a balanced incomplete block design.

Table 8 *Changes in plasma levels of salbutamol (ng/ml)*

Subject	*Dose*		
	1·5 mg	*3·0 mg*	*7·5 mg*
1	0		2·7
2	0·6		2·3
3	0		1·4
4	0·6		3·1
5		2·3	2·4
6		1·6	2·2
7		1·1	2·4
8		1·7	3·6
9	0	−0·2	
10	0	1·4	
11	0·2	0·7	
12	−0·1	0	
Mean	0·2	1·1	2·5
(SE)	(0·1)	(0·3)	(0·2)

In five of the subjects salbutamol was detected in the plasma before the morning treatment on both sampling occasions. In no subject was salbutamol detectable before medication on just one occasion. Whether this finding was caused by slow elimination of salbutamol absorbed the night before or consistent self-administration in the early morning we are unable to tell.

An analysis of variance was carried out on these data and demonstrated a dose-related increase in plasma levels ($p < 0·005$). There was no significant difference between absorption of the 3·0 mg dose compared to 1·5 mg although absorption of the 7·5 mg dose was significantly different from the other two ($p < 0·03$).

Discussion

We have demonstrated a dose-related response in terms of both FEV_1 and PEFR changes to doses of salbutamol nebuliser solution from 1·5 mg to 7·5 mg. Thus to achieve the greatest bronchodilatation the highest tolerated dose of salbutamol should be given. However, a consistently satisfactory therapeutic response can be achieved with a 3·0 mg dose or even less. Thus, for example, in the morning the median response for the 3·0mg dose was 25% and 24% for the change in FEV_1 and PEFR respectively (the

corresponding mean changes were 32% and 30%). In several of our patients the response to salbutamol decreased progressively over the four study days as they improved clinically and these figures are, therefore, probably an underestimate of the bronchodilator capacity of the 3·0 mg dose.

In terms of side-effects, however, the incidence of tremor and palpitations, reflecting systemic absorption of salbutamol, was about twice as great with the 7·5 mg dose as with 3·0 mg but it is at the 3·0 mg dose level that side-effects and drug absorption seem to be becoming evident. Similarly, pulse rate changes seem to be becoming significant at the 3·0 mg dose but are particularly evident at 7·5 mg.

From our data, therefore, we would suggest that, if a high dose of salbutamol respirator solution causes unacceptable side-effects, then the treatment should not be stopped as is now frequently done. Instead a smaller dose of salbutamol should be given. In general 3·0 mg of salbutamol respirator solution may be the optimal dose.

References

[1] Tattersfield AE, McNicol MW. Salbutamol and isoprenaline. A double-blind trial to compare bronchodilator and cardiovascular activity. *N Engl J Med* 1969;**281**: 1323-6.

[2] Lawford P, Jones BJM, Milledge JS. Comparison of intravenous and nebulised salbutamol in initial treatment of severe asthma. *Br Med J* 1978;i:84.

[3] Williams S, Seaton A. Intravenous or inhaled salbutamol in severe acute asthma? *Thorax* 1977;**32**:555-8.

[4] Martin LE, Rees J, Tanner RJN. Quantitative determination of salbutamol in plasma, as either its trimethylsilyl or t-butyldimethylsilyl ether, using a stable isotope multiple ion recording technique. *Biomed Mass Spectrom* 1976;**3**:184-90.

[5] Hollander M, Wolfe DA. *Non parametric statistical methods*. New York: Wiley, 1973:138-58.