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Nebulized Salbutamol (Asmasal®) in Thai Children with Asthma: Comparison of Three Doses.

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SUMMARY **Eleven moderate-to-severe asthmatic children 5-11 years of age who were in stable condition were given (randomly, double-blind) nebulized salbutamol sulfate (Asmasal®) inhalation therapy at doses of 0.1, 0.2 and 0.3 mg/kg body weight on separated days. All three doses of nebulized solution resulted in clinical improvement and improvement of lung function (FEV_1, FVC, PEFR and $FEF_{25-75\%}$). A dose of 0.3 mg/kg produced greatest improvement and longest duration of improvement in FEV_1 and PEFR, but the change was statistically significant only in PEFR at 60 minutes ($p < 0.05$). Five children experienced mild tremors. There were no significant changes in heart rate or blood pressure at any dose. It is concluded that a nebulized solution of salbutamol sulfate at a dose of 0.1-0.3 mg/kg is useful for treatment of asthma in Thai children, with very mild side effects.**

Nebulized selective beta-2 sympathomimetic agents (salbutamol, terbutaline, fenoterol and bitolterol) are among the first line treatment drugs for acute asthma in children.[1,2] The advantage of administration of these drugs by inhalation is that the maximum bronchodilator response can be attained rapidly and with far fewer side effects than by injection or oral administration.[2-5] There is continuing disagreement over the optimum dose of inhaled beta adrenergic bronchodilator.[6-9] Too small a dose may not give the maximum bronchodilator response, but too large a dose may be associated with greater cost and systemic side effects such as tremor and palpitations. The doses of salbutamol used in former studies have been in the range of 0.1-0.3 mg/kg body weight.[8-10] The optimum frequency of drug administration is also still unsettled.

Presently, beta-2 adrenergic bronchodilator solution is widely used in Thailand but its cost is high. Asmasal® (Silom, Thailand) which consists of 0.5% salbutamol sulfate inhalation solution, is much cheaper. If this inhalation solution is effective at the same dose as the bronchodilator solution, it will be useful. There is no information about the effectiveness of this medication in Thai children although it has been used by many physicians. The aim of this study is to study the efficacy, dose response characteristics and side effects of nebulized Asmasal® solution in Thai children with asthma.

MATERIALS AND METHODS

Materials

Thai children with moderate-to-severe asthma who were in stable condition were included in the study. Their baseline force expiratory volume in one second (FEV_1) was within 45-85% of predicted value and FEV_1 increased at least 15% of the baseline value after 15 minutes of metered dose of aerosolized salbutamol (Ventolin® : salbutamol sulfate BP 5 mg/ml respiratory solution, Glaxo). The patients had no hypersensitivity to salbutamol or systemic diseases, and did not have any acute attack of asthma or upper respirtory tract infection 10 days before or during the study.

The respiratory solution studied (Asmasal® , Silom, Thailand) was

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0.5% salbutamol. The composition of 1 ml of the solution was : salbutamol sulfate (5 mg), monobasic sodium phosphate buffer, benzalkonium chloride (preservative), distilled water to 1 ml. The solutions were administered via a Hudson nebulizer with face mask. The lung function test was performed with a Respiradyne spirometer (Sher - wood Medical, USA).

Methods

The study was randomized, double-blind, three-way cross over. Each patient received all the 3 concentrations of Asmasal® at random on the first day, then cross at random to the other 2 concentrations on the following days. The patients included into the study were explained the details of the study and parents' written consent were obtained. The study was approved by the Human Ethics Committee Siriraj Hospital. Theophylline was stopped at least 24 hours before the day of testing. Beta adrenergic bronchodilator was stopped at least 12 hours before the day of testing and anticholinergic drug was stopped at least 72 hours before. Inhaled steroid, inhaled cromolyn and oral ketotifen were continued.

The study was carried out on 3 separated study days using one dose (0.1, 0.2 or 0.3 mg/kg body weight; not more than 12 mg totally) on each day. The medication was prepared and diluted with 0.9% sodium chloride solution to 4 ml by a person who was not involved in the study. Parents, patients, and investigators were unaware of the doses. On each study day, the patient had FEV_1 between 45-80% of predicted value and the difference between days was not more than 25%. If FEV_1 was different by more than 25%, the study was postponed to the next day and the whole study period was not more than 7 days for each subject. At 0900 hours, salbutamol solution (Asmasal®) was nebulized through a Hudson nebulizer with face mask with oxygen flow 6-7 l/minute for 10-15 minutes by one of investigators who did not know the drug doses. The lung function test [included force expiratory volume in 1 second (FEV_1), force vital capacity (FVC), peak expiratory flow rate (PEFR) and force expiratory flow rate of 25-75% percent ($FEF_{25-75\%}$)], heart rate, respiratory rate and blood pressure were recorded at 0, 15, 30, 60, 90, 120, 180, 240 and 360 minutes.

Side effects such as tremor, palpitation, chest discomfort and dizziness were asked and recorded just before the lung function tests performed.

Analysis of data

Pulmonary function data were analyzed as percent increase over baseline levels. The formula to calculate percent increase in each lung functon is shown as the example of FEV_1 at 15 minutes:

Percent increase of FEV_1 at 15 minutes

$$= \frac{A-B}{B} \times 100$$

where A = FEV_1 at 15 minutes
and B = FEV_1 base line (same day).

These changes in lung function, heart rate, respiratory rate and blood pressure were analyzed by analysis of variance (ANOVA). A p-value of < 0.05 was considered statistically significant.

RESULTS

Eighteen Thai children with asthma aged 5 to 11 years were

Table 1. Initial clinical characteristics of the 11 study patients.

Characteristics	Results
Age (mean years ± SD)	9.1 ±2
Sex male : female	9 : 2
Duration of asthma (mean years ± SD)	4.3 ±1.8
Medication used before study	
Oral theophylline	10
Oral $Beta_2$ agonist	6
Inhale $Beta_2$ agonist	7
Inhale cromolyn sodium	3
Oral ketotifen	1
Inhale steroid	6
Mixture stramonium compound	5
None	1
FEV_1 (mean% of predicted value ± SD)	63.6 ±8.9
FVC (mean% of predicted value ± SD)	71.1 ±10.9
PEFR (mean% of predicted value ± SD)	40.8 ±6.7
$FEF_{25-75\%}$ (mean% of predicted value ± SD)	20.3 ±6.1
Heart rate (mean No. beats/min ± SD)	100.7 ±8.9
Respiratory rate (mean No. beats/min ± SD)	21.1 ±3.1
Blood pressure (mean mm Hg ± SD	
Systolic	94.8 ±8.9
Diastolic	55.5 ±6.3

initially included in the study, but four of them were excluded because of acute asthmatic attacks during the study. Three others were excluded because the differences among 3-day baseline FEV_1 values were more than 25%, leaving only data from 11 patients to be analyzed. Initial clinical characteristics of the patients are shown in Table 1. The analysis of lung function data showed that the peak times of mean percent increase of FEV_1 for doses of 0.1, 0.2 and 0.3 mg/kg body weight were at 90, 30 and 60 minutes, respectively, as shown in Fig. 1. The dose of 0.3 mg/kg body weight showed the highest increase in FEV_1 from the baseline level most of the time monitored, but the differences were not statistically significant. At 360 minutes, the mean percent increase in FEV_1 was more than 15% for all the three doses. Peaks of mean percent increase of FVC for 0.1, 0.2 and 0.3 mg/kg body weight doses were at 120, 30 and 30 minutes, respectively, as shown in Fig. 2. Peaks of mean percent increase of PEFR for doses of 0.1, 0.2 and 0.3 mg/kg body weight were at 30, 15 and 60 minutes, respectively, as shown in Fig. 3. The dose of 0.3 mg/kg showed highest mean percent increase of PEFR at all times monitored, but the significant difference from other doses was shown only at 60 minutes ($p < 0.05$). At 360 minutes, the mean percent increase of PEFR for 0.3 mg/kg was approximately 50% while those of 0.2 and 0.1 mg/kg were approximately 25%. Peak mean percent increases in $FEF_{25-75\%}$ for 0.1, 0.2 and 0.3 mg/kg were at 90, 30 and 60 minutes, respectively, as shown in Fig. 4. There was no significant difference among the mean percent increases in $FEF_{25-75\%}$ among the three doses at any time.

Maximum improvement of lung functions after Asmasal® nebulization is shown in Table 2. At the end of the study time (360 minutes), the dose of 0.3 mg/kg showed the highest means in FEV_1, PEFR and $FEF_{25-75\%}$ while the dose of 0.1 mg/kg showed the highest mean FVC.

Table 2. Maximum improvement of lung functions after Asmasal® nebulization.

	Maximum improvement (%)		
	0.1 mg/kg	0.2 mg/kg	0.3 mg/kg
FEV_1	43 ±8	41 ±11	52 ±8
FVC	28 ±15	20 ±8	25 ±15
PEFR	73 ±6	68 ±7	91 ±7
$FEF_{25-75\%}$	105 ±10	85 ±15	100 ±8

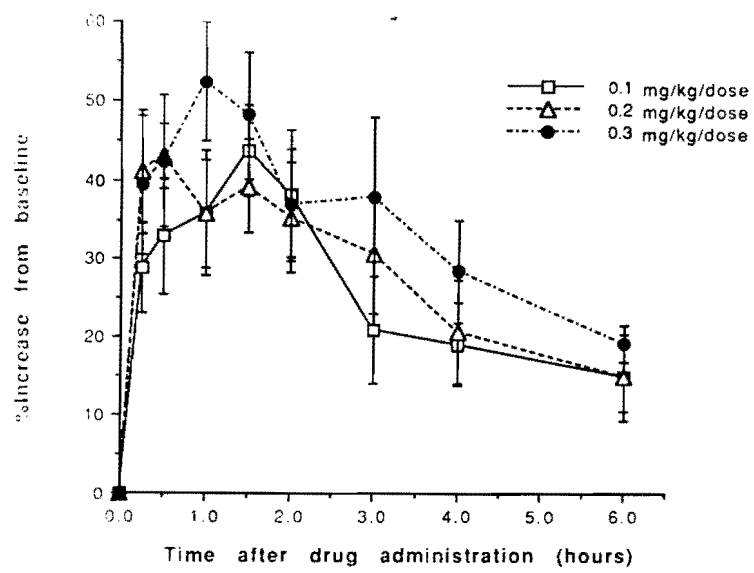

Fig. 1 Mean percentage increase of FEV_1 at various intervals up to 6 hours after nebulization. Bars indicate standard error of means.

Changes in heart rate after Asmasal® administration at various intervals up to 6 hours are shown in Fig. 5. The increase in heart rate after the dose of 0.3 mg/kg was higher than those for 0.2 and 0.1 mg/kg, but the differences were not statistically significant. The maximum increase in heart rate was observed with the dose of 0.3 mg/kg at 30 minutes. The heart rate increase seemed to be dose-related. Changes in respirtory rate after Asmasal® administration are shown in Fig. 6. There was a slight increase and also decrease in respiratory rate during the treatment, but the changes were not statistically significant. Changes in systolic and diastolic blood pressures are shown in Fig. 7. There was slight increase in systolic blood pressure from the baseline

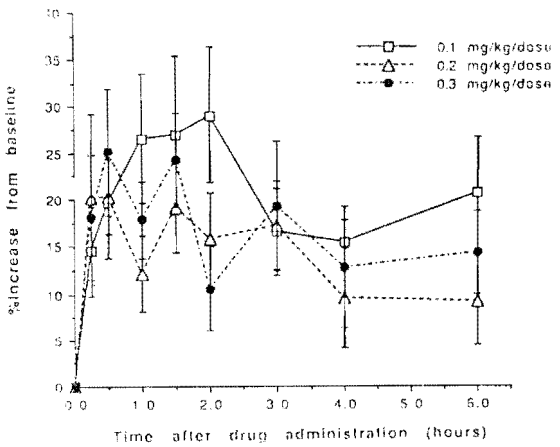

Fig. 2 Mean percentage increase of FVC at various intervals up to 6 hours after nebulization. Bars indicate standard error of of means.

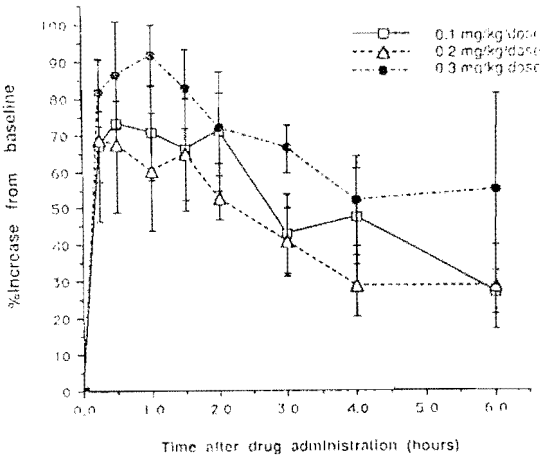

Fig. 3 Mean percentage increase of PEFR at various intervals up to 6 hours after nebulization. Bars indicate standard error of means.

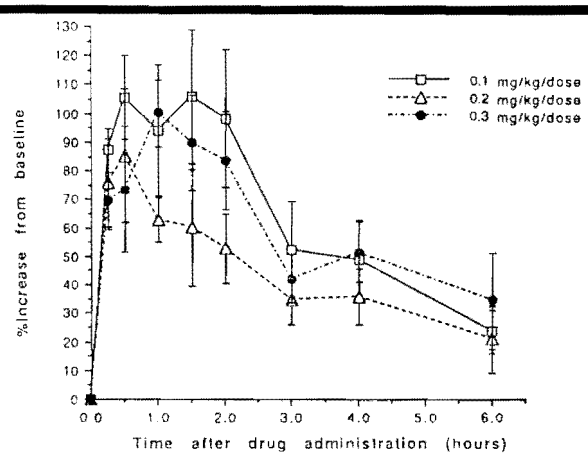

Fig. 4 Mean percentage increase of $PEF_{25-75\%}$ at various intervals up to 6 hours after nebulization. Bars indicate standard error of means.

level after all three doses but the change was not statistically significant. There was a slight increase and decrease in diastolic blood pressure from the baseline after Asmasal® administration but also the change was not significant.

An adverse clinical reactions were found in 5 out of 11 patients. Mild tremor was found in 2 cases at the dose of 0.1 and 0.2 mg/kg at 15 and 30 minutes and in 5 cases at the dose of 0.3 mg/kg at 15 minutes. Two patients who received the dose of 0.3 mg/kg had very mild tremors for 6 hours. One of the patients had palpitations 15 minutes after administration of 0.3 mg/kg of Asmasal® respiratory solution but the symptoms were mild and well tolerated. No patient had to interrupt or stop participation in the study because of the side effects. All of them accepted that this respiratory solution was effective in the treatment of asthma and easily tolerated.

DISCUSSION

Asthma is a common disease in Thai children; its cumulative prevalence in Thai children aged 6-12 years has been found to be 4.3%.[11] Inhalation of beta-2 sympathomimetic agents is the preferred treatment. The main benefit of inhalation therapy is that high levels of the drug are concentrated at the site of action, giving the desired therapeutic result with minimal side effect. The nebulized dose must be higher than the dose used in the oral or injected route because only about 10% of the dose actually reaches the lung.[2,12,13] The total diluted nebulized solution used was 4 ml and O_2 flow was 6-7 l/minute to ensure optimum deposition of the drug particles in the lung, as prescribed in a previous study.[14]

Our pilot study showed that Asmasal solution (0.5% salbutamol sulfate inhalation solution) was effective as a bronchodilator with-

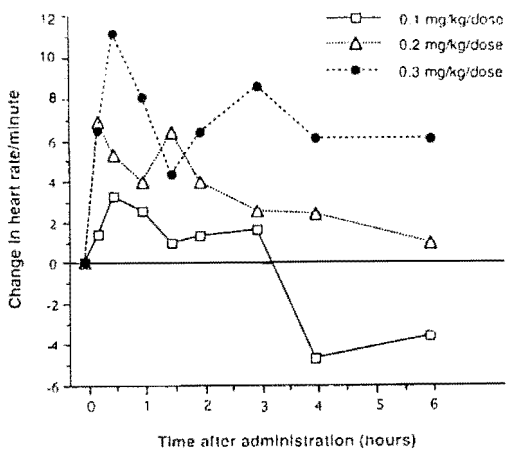

Fig. 5 Mean change in heart rate at various intervals up to 6 hours after nebulization.

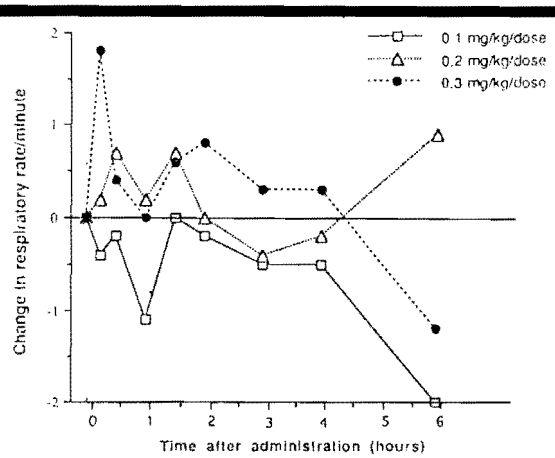

Fig. 6 Mean change in respiratory rate at various intervals up to 6 hours after nebulization.

out side effects even at the high dose, 0.3 mg/kg body weight. This study showed that the solution has good bronchodilating effect at nebulized doses of 0.1-0.3 mg/kg by showing significant improvement in lung functions. The bronchodilator effect was recorded shortly after the neubulized solution was given. At 15 minutes the lung functions increased rapidly and reached a peak response at about one hour. A previous study showed that the action started before 15 minutes and peaked at 30-60 minutes.[15] The present study showed that a dose of 0.3 mg/kg of Asmasal® resulted in the greatest improvement in overall lung function but a significant improvement was found only in PEFR at 60 minutes ($p < 0.05$). This supports previous studies which showed that patients who received higher dose had significantly greater improvement in FEV_1, FVC, wheeze score and hospitalization rate than the lower dose group.[8,9] Some reports have shown a dose-related bronchodilator response increase in FEV_1 and PEFR after nebulized salbutamol.[13,16] The dose of 0.3 mg/kg also showed a longer duration of improvement in FEV_1 and PEFR. At 360 minutes after nebulized solution the FEV_1 and PEFR showed significant increases from

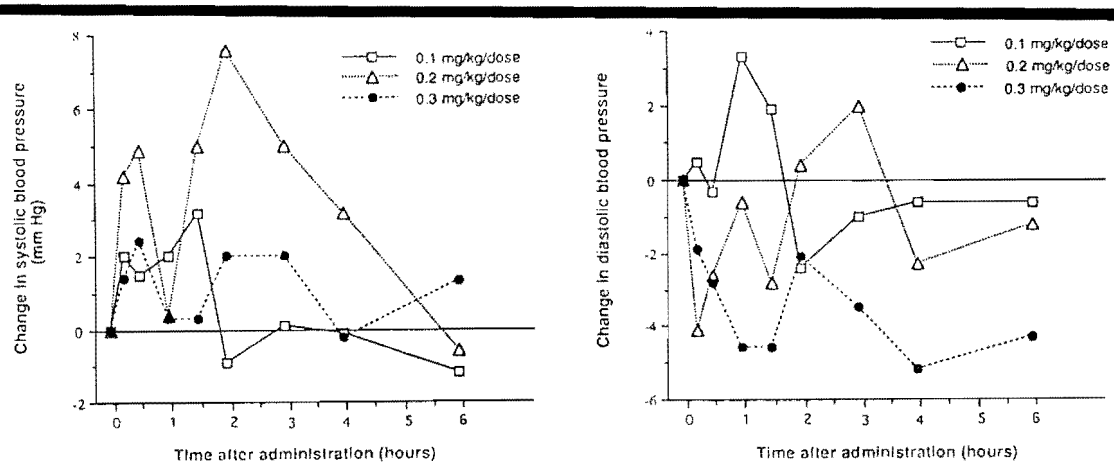

Fig. 7 Mean change in systolic blood pressure (a) and diastolic blood pressure (b) at various intervals up to 6 hours after nebulization.

baseline levels. The increase in FEV_1 after a dose of 0.3 mg/kg was more than 20% while for 0.1 and 0.2 mg/kg it was more than 15%. The increase of PEFR after the dose of 0.3 mg/kg was moe than 50% while 0.1 and 0.2 mg/kg caused approximately 25% increase. This result supports the previous studies which found that suboptimal doses of beta-2 adrenergic agents produced adequate bronchodilator effects, but with reduced duration.[1,17]

The reported side effects of salbutamol are apnea, tremor, tachypnea, palpitation, tachycardia.[15,16] The side effects have the same duration as the bronchodilating effect and are related to the dose and the plasma concentrations of salbutamol.[16,18,19] Most of the side effects reported resulted from the oral route or injection. One report has shown that the increase in pulse rate from administration by the systemic route depends on the amount reaching the lung.[20] The side effects from the aerosolized or nebulized route are minimal, even with high or repeated doses.[15-17,21-23] The dose of 0.3 mg/kg showed the highest increase in heart rate, still higher than the baseline level at 360 minutes. The maximum increase in heart rate was at 30 minutes after which it declined slowly. Although most patients showed increases in heart rate, they tolerated it well so the inhalation could be continued. The side effects were recorded in 5 of the 11 patients, which all had tremor at the dose of 0.3 mg/kg. Two patients had tremor with all three doses, and one had palpitation. The side effects started at 15 minutes but they were very mild and well tolerated. Salbutamol can cause tachycardia by β_2-stimulated vasodilatation and subsequent reflex tachycardia.[9]

The severity of side effects also depends on individual factors such as illness-related stress, level of anxiety and personal sensitivity to the drug.[9] Tremor was the most common side effect in our study similar to a previous one.[9] Another study showed that most side effects such as tremor, palpitation and tachycardia occured within the first 80 minutes and thereafter the heart rate stabilized or began to decline.[24] This may have been due to a beta receptor desensitization effect.

We conclude from our study that nebulized Asmasal solution at the doses of 0.1-0.3 mg/kg produce significant improvement in lung function in children with asthma who were in stable condition. The highest dose, 0.3 mg/kg body weight showed the longest duration of improvement in lung function, and also duration of side effects. The side effects were mild and well tolerated. The respiratory solution is useful in the treatment of Thai children with asthma.

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Preliminary Notice

Combined Inaugural Meeting of the Federation of Immunological Societies of Asia/Oceania (FIMSA)

and the

14th. Annual Scientific Meeting of the Australasian Society for Immunology

To be held in the Adelaide Convention Centre, Adelaide, South Australia, Australia.

From the 1st. to 6th. of December, 1996.

The conference will cover all aspects of immunology, but will focus on immunity to infectious agents, immunodiagnosis and vaccine development.

This meeting will feature an array of keynote addresses presented by leading international scientists.

Adelaide is a modern provincial capital easily accessable from Asia and the Pacific, and with direct links to other major tourist destinations and capital cities within Australia. This well-planned city is situated on a fertile coastal plain fringed by a range of hills and is characterized by spacious public parks and mixture of attractive 19th. and 20th. century architecture. Adelaide enjoys a pleasant temperate climate and December is the beginning of a summer which is typically warm and dry. Accommodation of every standard is plentiful in Adelaide - from five star hotels to budget tourist standard and everything in between. In addition, located just a short, attractive walk from the conference venue are several university residential colleges which will offer economical accommodation to delegates.

Those attending this meeting will have the opportunity for extensive pre- or post- conference sightseeing in our unique Australian environment. Adelaide is well situated to enjoy the safe sandy beaches, rugged coastlines and mountain ranges, temperate wetlands, deserts, river cruises, wildlife, deep-sea fishing and sporting facilities that South Australia has to offer. Adelaide is also at the centre of wine grape-producing regions which have made Australian wines famous world-wide. National treasures such as the Great Barrier Reef and Uluru (Ayer's Rock) are also within easy reach via regular airline services.

You are invited to plan ahead for what promises to be a most rewarding meeting.

Further enquiries can be directed to Dr. Lindsay Dent, Dept. of Microbiology and Immunology, Univesity of Adelaide, North Tce., Adelaide, South Australia, AUSTRALIA, 5005.
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