THERAPEUTIC REGIMES FOR ACUTE BRONCHIAL ASTHMA

V Anantharaman

ABSTRACT

No uniform guidelines currently exist for the initial drug therapy of asthma or for the criteria to assess efficacy of initial therapy. A study with 71 subjects aged between 15 and 40 years was conducted to compare the usefulness of three commonly used asthma treatment regimes, viz subcutaneous adrenaline, nebulised salbutamol and intravenous aminophylline. Parameters used to monitor response were pulse rate (PR), respiratory rate (RR), Peak Expiratory Flow Rate (PEFR) and Patient's Subjective Assessment Scale (PSAS).

All patients in the three treatment groups were comparable at pre-treatment, except for the Salbutamol group which appeared to have asthma of a milder severity based on PSAS scores alone. Following treatment, improvements were noted in Peak Flow Rate and PSAS. These improvements were greatest in those groups treated with salbutamol and adrenaline ($p = 0.04$ for PEFR and 0.01 for PSAS). Salbutamol treated patients also had significant improvements in Respiratory Rate ($p < 0.05$). The results were not conclusive as to whether adrenaline or salbutamol was the superior drug.

Salbutamol and adrenaline are preferred to aminophylline in the initial treatment of acute bronchial asthma.

Keywords : subcutaneous adrenaline, nebulised salbutamol, intravenous aminophylline, Peak Expiratory Flow Rate, Patient's Subjective Assessment Scale.

SINGAPORE MED J 1993; Vol 34: 534-537

INTRODUCTION

The initial management of acute bronchial asthma has undergone many changes over the last century. Inhalation of chloroform or stramonium fumes[1], administration of narcotics, sedatives, ether enemas and caffeine or strong coffee have given way to the introduction of subcutaneous adrenaline in 1903[2], administration of inhaled adrenaline 30 years later[3] and subsequent use of theophyllines, adrenergic agonists and corticosteroids. All these various modes of treatment have had but one aim: the prompt alleviation of symptoms with minimal side-effects of therapy.

In Singapore, three modes of therapy have, for a number of years, dominated the initial emergency department management of patients with an acute asthmatic attack. These are nebulised beta-agonists, intravenous aminophylline and subcutaneous adrenaline. There have been no clear guidelines on which of these are the drug of choice. Rather, individual preferences which were ruled by subjective impressions and ease of delivery dictated the choice of drug and the route of administration. The purpose of this study was to determine the best of these three regimes based on simple, easily available criteria.

There is an absence of universally accepted uniform criteria for a decision on optimal drug therapy for this condition. The author has previously reported that improvement in the Patient's Subjective Assessment Scale - a parameter that employs a scale of 10 to 0 in decreasing order as an index of severity of acute asthma - was more predictive of patient outcome and disposal than improvements in other parameters such as peak expiratory flow rate, respiratory rate and pulse rate[4].

This study was designed to evaluate the efficacy of the three commonly used regimes in the treatment of an acute asthmatic episode using the parameters just mentioned.

Department of Accident & Emergency
Singapore General Hospital
Outram Road
Singapore 0316

V Anantharaman, MBBS, MRCP (UK), FAMS
Consultant Physician

PATIENTS AND METHODS

This study was carried out by a single observer over a six- month period at the Accident & Emergency (A&E) Department of the Singapore General Hospital. Patients between the ages of 15 years and 40 years presenting with an acute attack of bronchial asthma and attended to by this observer were entered into this study. Consent was obtained from each patient and the purpose of the study was explained to each patient.

All such patients were randomised to one of three therapeutic regimes: viz subcutaneous adrenaline 1 mg over a period of 10 minutes (Group A), nebulised salbutamol 10 mg over a period of 10 minutes (Group B), and intravenous aminophylline 250 mg over a period of 10 mins (Group C). All those who were on chronic theophylline therapy at the time of presentation to the A&E Department and assigned to Group C were again randomly reassigned to either of Groups A or B.

During the ten minute duration of administration of therapy, every patient was maintained in the sitting posture with oxygen given at a rate of 5 litres/minute by mask, which was continued for a period of at least 20 minutes following cessation of therapy.

The study population was evaluated for the following parameters prior to initiation of therapy and at 10 minutes and at 20 minutes following completion of the treatment procedures:

a. Pulse rate (PR) for one full minute.
b. Respiratory rate (RR) for one full minute.
c. Peak expiratory flow rate (PEFR) in litres/min whereby the best of three attempts using a Mini-Wright Peak Flow Meter was taken as the patient's PEFR at any particular point of time.
d. Patient's subjective assessment scale (PSAS) – with the patient deciding his/her severity of asthma at a point of time on a scale of 0 to 10, with the value "0" being complete normalcy and the value "10" being the worst state of breathlessness the patient could have been in.

The determination of these indices was by a nursing staff member of the A&E Department.

Following the third set of readings, a clinical evaluation of the patient's clinical condition was made by the single observer and a decision was made as to whether to admit the patient for in-hospital care or to discharge the patient on account of significant improvement.

Statistical Analysis

The differences between the groups were analysed using analysis of variance (ANOVA). Paired and unpaired t-tests were utilised, where indicated, to evaluate differences between two populations that were normally distributed. For populations that were not normally distributed, non-parametric tests (Mann-Whitney test) were performed. All data are expressed as mean ± standard deviation. All statistical analyses were performed using the RSI Statistical Package (Bolt, Beranek and Newman, Cambridge, Massachusetts).

RESULTS

The characteristics of the 71 patients who participated in the study are shown in Table I.

Further analysis by non-parametric testing indicated that the p value for PSAS was owing to a low PSAS of Group B which was responsible for differences between Groups A and B ($p < 0.05$) and between Groups B and C ($p < 0.01$). Groups A and C were statistically comparable ($p = 0.192$). This indicates that Group B (by PSAS measurement only) had acute bronchial asthma of lesser severity. The other parameters used could not, however, point out any obvious significant difference between the three groups.

At ten minutes following the completion of therapy, no significant differences were observable, either in the pulse rate (Table II) or the respiratory rate (Table III) of the three groups of patients and in addition, no significant change had occurred in the pulse rate $p = 0.084$ as a result of treatment.

This was not the case, however, with the PEFR (Table IV) and the PSAS (Table V) which demonstrated significant changes. These changes indicated, that even as early as ten minutes following cessation of therapy, though no significant difference was noted between treatment regimes A and B, each of these 2 regimes demonstrated a greater improvement in both peak expiratory flow rate ($p = 0.0001$) and in the patient's subjective condition ($p = 0.0001$), when compared to Group C.

At twenty minutes post-therapy, the changes observable in the three groups of patients were even more remarkable. Although the pulse rates of all three groups of patients were close to each other as shown in Table II, the improvement in pulse rate from pre-treatment levels was significant for Groups A and C. No adverse cardiovascular effects were noted in any of the 71 patients during the period of the study.

As for the respiratory rate, all groups reported significant fall at 30 mins post-treatment from the pre-treatment values as shown in Table III. In addition, there was a significant difference between the absolute respiratory rate of Group B at this time period and the respiratory rate of Group A ($p = 0.05$) and Group C ($p = 0.02$).

The PEFR improved tremendously for all three groups of patients as shown in Table IV. The change was greatest for Group B (90%) followed by Group A (73.2%) and Group C (50.2%). The PEFR achieved by patients in Groups A and B was significantly higher than those achieved by patients in Group C (ANOVA $p = 0.04$). The difference in the PEFR between Group A and Group B did not reach statistical significance ($p = 0.70$). Group A performed better than Group C ($p = 0.04$). The salbutamol group also responded better than Group C ($p < 0.01$).

Table I – Characteristics@ of study population

Pre-treatment Characteristic	Group A (Adrenaline)	Group B (Salbutamol)	Group C (Aminophylline)	ANOVA+ p
Sample size	27	17	27	–
Sex – Male/Female	15 / 12	8 / 9	11 / 16	–
Age (years)	27.1 ± 6.8	23.6 ± 6.0	29.4 ± 6.7	NS
Pulse rate (beats/min)	102.8 ± 19.4	104.6 ± 21.1	108.6 ± 17.6	0.53 (NS)
Respiratory rate (respirations/min)	28.3 ± 6.4	25.2 ± 4.5	27.4 ± 4.2	0.16 (NS)
*PEFR (litres/min)	169.6 ± 134.4	163.5 ± 59.8	145.9 ± 71.5	0.66 (NS)
** PSAS	7.6 ± 1.9	6.8 ± 1.0	8.2 ± 1.8	0.03

@ : All are mean values ± Standard Deviation
*PEFR : Peak Expiratory Flow Rate
** PSAS : Patient's Subjective Assessment Scale
+ANOVA : Analysis of Variance

Table II – Response of pulse rate* to treatment

Group	0 min	20 mins	30 mins	$P_{0\ 30}$@
Group A (Adrenaline)	102.8 ± 19.4	100.0 ± 19.7	95.3 ± 19.4	0.01
Group B (Salbutamol)	104.6 ± 21.1	105.6 ± 21.8	99.8 ± 17.9	0.127 (NS)
Group C (Aminophylline)	108.6 ± 17.71	101.5 ± 24	98.4 ± 20.8	0.02
+ANOVA p	0.53 (NS)	0.60 (NS)	0.73 (NS)	

* : Readings are in beats/min
P_{0-30}@ : p value of difference between values at 0 min and values at 30 mins
+ANOVA : Analysis of Variance p compares the pulse rates amongst all three treatment groups at the particular point of time

Table III – Response of respiratory rate* to treatment

Group	0 min	20 mins	30 mins	0 – 30	P_{0-30}@
Group A (Adrenaline)	28.3 ± 6.4	24.1 ± 5.5	22.9 ± 6.6	5.4 ± 6.5	0.001
Group B (Salbutamol)	25.2 ± 4.5	20.5 ± 6.0	18.5 ± 4.1	6.7 ± 4.1	0.0001
Group C (Aminophylline)	27.4 ± 4.2	24.7 ± 6.4	23.5 ± 5.4	3.8 ± 5.1	0.001
ANOVA p**	0.16	0.07	0.009	0.23	

* : Readings are in respirations/min
** : ANOVA p compares the respiratory rate amongst all three treatment groups at the particular point of time

Table IV – Response of peak expiratory flow rate* to treatment

Group	0 min	20 mins	30 mins	0 – 30
Group A (Adrenaline)	169.6 ± 134.4	272.2 ± 141.4	293.7 ± 156.7	124.1 ± 75.7
Group B (Salbutamol)	163.5 ± 59.8	302.4 ± 103.6	310.6 ± 11.35	147.1 ± 90.7
Group C (Aminophylline)	145.9 ± 71.5	196.3 ± 95.9	219.2 ± 100.6	70.0 ± 62.5
ANOVA p**	0.66 (NS)	0.01	0.04	0.003

* : Readings are in respirations/min
** : ANOVA p compares the respiratory rate amongst all three treatment groups at the particular point of time

Table V – Response of patient's subjective assessment state to treatment

Group	0 min	20 mins	30 mins	0 – 30
Group A (Adrenaline)	7.6 ± 1.9	3.1 ± 2.0	1.9 ± 1.8	5.7 ± 2.4
Group B (Salbutamol)	6.8 ± 1.0	3.3 ± 1.2	2.2 ± 1.9	4.6 ± 2.1
Group C (Aminophylline)	8.2 ± 1.8	5.0 ± 2.9	3.7 ± 2.6	4.5 ± 2.3
ANOVA p*	0.03	0.007	0.01	

* : ANOVA p compares the respiratory rate amongst all three treatment groups at the particular point of time

All three treatment groups showed improvements in the PSAS score with therapy. However, when considering changes in the PSAS with treatment, Group A (adrenaline) showed the greatest improvement. This change was significant when compared to the other 2 treatment groups ($p = 0.036$).

The only significant correlation between the four parameters was that between the increase in PEFR and the improvement in PSAS which achieved a correlation coefficient of 0.39 ($p = 0.001$).

Amongst the study population, 22 out of 71 needed further in-hospital care as assessed by the lone observer's clinical judgement (Table VI). On further analysis, it was found that 14.8% of Group A patients, 35.3% of Group B patients and 44.4% of Group C patients required hospital admission. The only significant difference was in the admission rates between Groups A and C ($p = 0.02$).

DISCUSSION

This study was confined to a population aged between 15 and 40 years of age for the following reasons:

a. Children below 15 years of age were felt to be less able to subjectively assess the degree of severity of their asthmatic attacks than those above that age.
b. Children below 15 years were thought to be less able to co-operate fully with the technique of obtaining peak flow rate readings than adults.
c. Persons over 40 years of age were felt to be more prone to hypertension, coronary artery disease, cigarette smoking and its irreversible effects on the airway. The response of the various parameters to the therapeutic regimens would be expected to be modified by the ability of the cardiovascular and respiratory systems to be affected by the above-mentioned changes that are generally more rampant in the above 40 year age group.

This study clearly showed that for patients in the 15 to 40 years age group, adrenaline, salbutamol and aminophylline did not produce an adverse cardiovascular response when used in the initial management of acute bronchial asthma. That there was no significant tachycardia, but instead a slight fall in pulse rate (which did reach statistical significance) was perhaps owing to:

Table VI – Disposition of asthmatic patients as a result of therapy

Group	Admissions	Discharges	Total
Group A (Adrenaline)	4	23	27
Group B (Salbutamol)	6	11	17
Group C (Aminophylline)	12	15	27
Total	22	49	71

a. Relief of hypoxia which would have the effect of increasing the myocardial oxygen supply and therefore decreasing the myocardial work load, thus mitigating against the direct sympathomimetic effects of all three agents used.
b. Relief of anxiety and physical work of hyperventilation brought about by the improvement in severity of the asthmatic attack which would have further mitigated against the direct sympathomimetic effects of adrenaline, salbutamol or aminophylline.

The study shows that nebulised salbutamol or subcutaneous adrenaline may be superior to IV aminophylline as the initial drug of choice in the management of the acute attack of bronchial asthma. As to whether aminophylline should ever be considered in the initial management of bronchial asthma now that better drugs are available, Fitzgerald and Hargreave[5] are of the opinion that not only does aminophylline have a low therapeutic ratio, it is also potentially toxic, especially when factors such as age, coincidental heart failure, concomitant therapy with such agents as erythromycin, cimetidine and a history of cigarette smoking are taken into account. An analysis by Littenberg[6] of 13 adequately designed studies in patients with severe, acute asthma decided that there was no conclusive evidence for any marked beneficial effect of aminophylline. Rossing et al[7] have demonstrated that aminophylline did not confer any additional benefit when used with beta-agonists.

The question whether salbutamol is therapeutically more effective than adrenaline still remains open. Based on the results of this study:

a. Salbutamol produced a post-treatment respiratory rate significantly lower than that due to adrenaline. However, the absolute decrements were not significantly different. This could be because Group B started off with an average respiratory rate lower than (but not significantly) that of Group A. In addition, the problems encountered in perseverance of measurement of respiratory rate indices over a full minute can compromise the accuracy of this index.
b. Salbutamol produced a 90% rise in the Peak Expiratory Flow Rate as opposed to adrenaline which produced a 73% improvement ($p = 0.37$ NS). It is speculative to conclude that a larger sample size for Group B could have pushed this difference to mathematical significance.
c. The Patient's Subjective Assessment Scale (PSAS), which in a previous study[4] showed itself to be the most sensitive index of improvement for Acute Bronchial Asthma, gave a different picture. Patients treated with adrenaline not only began with a higher mean PSAS than those treated with salbutamol. The 20 minute post mean PSAS was lower in the adrenaline treated group when compared to that in the salbutamol group. Even then the difference in improvement in PSAS between these two groups was, though numerically greater for adrenaline treated patients (5.7 vs 4.6), not statistically significant ($p = 0.12$).
d. In-hospital admission rates also differed – the admission rate for patients treated with salbutamol being more than twice that in the adrenaline treated group. This difference again did not reach mathematical significance.

Therefore, while adrenaline appeared to tend towards a subjectively superior effect when compared with salbutamol, such a tendency could not stand mathematical significance testing nor could it be substantiated by objective clinical measurements. At this point we can only say that both agents appear to be equipotent in effect. It is also reassuring to note that adrenaline given for the treatment of bronchial asthma in a dose of 1.0 mg subcutaneously was extremely well tolerated by the 15-40 year old patient population.

It must however be remembered that adrenaline needs to be given under close supervision with intermittent advances of the syringe piston. Its potential cardiovascular side-effects in the elderly and in those with organic heart disease cannot be totally ignored. Adrenaline has been used successfully since 1951[8,9] for the treatment of acute severe asthma and continues to form a useful component of the drug armamentarium for acute bronchial asthma.

Salbutamol by nebulisation also requires supervision for maximal delivery of the drug to action sites in the bronchial tree. The patient should be advised to breathe deeply through the mouth and not be left unsupervised with a Venti-mask over the mouth and nose.

The decision between adrenaline and salbutamol must therefore be made after taking all the above factors into consideration. Doctor and nurse convenience cannot be the overriding factor.

The initial therapeutic agent is only one aspect of the overall management of the patient presenting to the Emergency Department with an acute attack of bronchial asthma. Other aspects of at least equal, if not more, importance are adequate and rapid assessment, early attention, oxygen therapy, hydration and the addition of other therapeutic agents or procedures if deemed necessary. The parameters used in this study form four simple, non-invasive, useful and easily measured indices. Their use as aids in the initial management of acute bronchial asthma should add a more scientific approach to the management of this common medical condition.

ACKNOWLEDGEMENT

I thank Dr Lim Swee Keng, Head, Accident & Emergency Department, Singapore General Hospital for his support of this project, Mrs Judy Teng for her excellent typing of the manuscript and the nursing staff of the Accident & Emergency Department for patiently assisting me in the conduct of this study.

REFERENCES

1. Dolen WK, Weber RW. Assessment and management of acute asthma. Ann Allergy 1989; 63:86-95
2. Bullowa JGM, Kaplan DM. On the hypodermic use of adrenalin chloride in the treatment of asthmatic attacks. Med News 1903; 83:787
3. Graeser JB, Rowe AH. Inhalation of epinephrine for the relief of asthmatic symptoms. J Allergy 1935; 6:415
4. Anantharaman V. A poor man's emergency assessment of bronchial asthma. Proceedings of the 6th World Congress on Emergency and Disaster Medicine, Hong Kong, 1989; 2:106-7 (Abstract)
5. Fitzgerald JM, Hargreave FE. The assessment and management of acute life-threatening asthma. Chest 1989; 95:888-94
6. Littenberg B. Aminophylline treatment in severe, acute asthma. JAMA 1988; 259:1670-84
7. Rossing TH, Fanta CH, Goldstein DH, Snapper JR, McFadden ER. Emergency therapy of asthma: comparison of the acute effects of parenteral and inhaled sympathomimetics and infused aminophylline. Am Rev Respir Dis 1980; 122:365-71
8. Freedman BJ. Adrenaline in status asthmaticus. Lancet 1955; ii:575
9. Broom B. Adrenaline in status asthmaticus. Lancet 1961; ii:1174