Asian Pacific Journal of Allergy and Immunology (1994) 12 : 1-6

Ease of Handling and Efficacy of Bricanyl Turbuhaler in Asian Asthmatic Children

Pakit Vichyanond[1], Phaiboolya Phanichyakarn[2], Azizi Hj Omar[3], Alfred Tam[4] and Ellick Wong[5]

SUMMARY **Ease of handling as well as efficacy of a new terbutaline inhalation device - Bricanyl Turbuhaler - were evaluated among eighty-six Asian children with mild to moderate asthma with a mean age of 8.7 years (range 5 to 14 years) in an open, non-comparative trial. Clinical evaluations were performed on four occasions, ie at the beginning of the run-in period, at the start of the study medication, after 2 weeks of treatment and after a total of 4 weeks of treatment. Appraisal of handling technique was performed by the investigator at the start and end of treatment. Peak expiratory flow rate (PEF) was determined at each visit. Diaries were also kept throughout this time; PEF and asthma symptom scores were recorded every morning and evening. Maximum scores for inhalation technique were achieved by 73% of patients after combined written and verbal instructions at the start of the study and 99% of patients achieved this score at the end of the 4 week treatment period with Bricanyl Turbuhaler. Assessment revealed that approximately 90% of the patients considered loading, inhalation and handling of the Turbuhaler device to be easy, and 90% considered it to be effective in affording symptom relief. Improvements in PEF and reductions in asthma symptoms were observed during the Bricanyl Turbuhaler treatment, as compared to baseline values. All patients tolerated the study medication well without any serious adverse events. We concluded that this group of Asian children were able to use this new "Turbuhaler" device of terbutaline without any difficulty. Moreover, the device was quite well received amongst most patients and positive clinical response was observed during the trial period.**

Selective β_2-agonists are the most effective means of therapy for the relief of acute asthmatic attack in children.[1,2] Due to several errors and problems patients had in handling pressurised metered-dose inhalers (MDI), particularly amongst children and elderly,[3-5] dry powder inhalers (DPI) have been developed to solve these shortcomings. The new "Bricanyl Turbuhaler", an inspiratory dry powder inhaler that contains 200 doses of pure powder of terbutaline sulphate, is among several of DPIs introduced into clinical use recently.[4] Each dose of the Turbuhaler medications can be easily loaded and handled by the patient and does not require coordination between activation and inhalation.[4] More importantly, Turbuhaler is effective also at low inspiratory flow which can be generated within the pediatric age range,[6] thus making this device optimal for use in children.

Since its introduction, the Turbuhaler device, particulary the Bricanyl Turbuhaler, has only been evaluated in caucasian children.[7-9] Questions regarding whether children of less developed countries and of less education such as from eastern Asia would be able to derive benefit from the device have been raised. We therefore, set out to determine the ability of Asian children with mild to moderate asthma in the handling of the Turbuhalers. In addition, symptom scores as well as peak expiratory flow rate and other clinical parameters were recorded during the study period to

from the [1]Faculty of Medicine Siriraj Hospital, Bangkok, Thailand, [2]Faculty of Medicine Ramathibodi Hospital, Bangkok, Thailand, [3]Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia, [4]Queen Mary Hospital, Hong Kong, [5]Astra E. Asia Regional Office, Singapore.

Correspondence : Pakit Vichyanond, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Bangkok 10700, Thailand.

gather preliminary data concerning the clinical efficacy of Bricany Turbuhaler amongst this group of patients.

MATERIALS AND METHOD

Patients and study design

The study was of an open, non-comparative, multi-centre design. Eighty-six children (56 males and 30 females) between the ages of 5 to 14 (mean ± SD = 8.7 ± 2.1) years old and with mild to moderate asthma, as classified according to the international consensus for the diagnosis and treatment of asthma,[10] were enrolled in the study. Exclusion criteria included hypersensitivity to beta-adrenergic drugs, and concomitant disease such as cardiovascular, renal and hepatic diseases. Forty-two children were from Siriraj Hosptial, Bangkok, Thailand, twenty-two from Ramathibodi Hospital, Bangkok, Thailand, sixteen from Queen Mary Hospital, University of Hong Kong, and six from the Faculty of Medicine, Universiti Kebangsaan, Kuala Lumpur, Malaysia. The study lasted 5 weeks with a one week run-in period and four weeks treatment with Bricanyl Turbuhaler (0.5 mg terbutaline sulphate) 3 times daily. All other previous treatments that patients received, except for other beta 2-agonist inhaler therapy (which was stopped at the initiation of the Bricanyl Turbuhaler treatment), were kept constant throughout the study. Concomitant anti-asthmatic treatments used amongst these patients were oral xanthines (n = 51), oral β_2-agonists (n = 26), oral anti-histamines (n = 6), inhaled corticosteroids (n = 21), carbocysteine (n = 2), stramonium mixture (n = 3), sodium cromoglycate (n = 5) and norephedrine (n = 1).

All patients were seen in the clinic at the beginning of the run-in period, at the start of Bricanyl Turbuhaler treatment when baseline measurements were made, and after 2 and 4 weeks of treatment with Bricanyl Turbuhaler. They were asked to refrain from taking any medications 5 hours preceeding each clinic visit. Inhalation techniques were assessed following the first written and verbal instructions for Turbuhaler from the investigator, at the start and end of active drug treatment. The assessment of inhalation technique comprised loading the inhaler in the upright position, exhalation (but not through Turbuhaler), inhalation from the Turbuhaler, and breath holding for 10 seconds. Each of these items was scored 0 to 1 for poor and good performance accordingly.

The patients' acceptance of Bricanyl Turbuhaler was appraised at the end of the study. All children were asked to state whether the loading, inhalation procedure and handling of the Bricanyl Turbuhaler was easy, neither easy nor difficult, or difficult. They were also asked whether the Bricanyl Turbuhaler was effective, neither effective nor ineffective, or ineffective. Peak expiratory flow rate (PEF) was measured at each clinic visit using a Mini-Wright peak flow meter and the severity of symptoms at each clinic visit was recorded. Diary cards were completed throughout the study by the children. PEF (morning and evening), as well as asthma symptom scores were recorded. Asthma symptoms were scored from 0 to 3 (0 = none, 1 = mild, 2 = moderate and 3 = severe symptoms). The number of extra doses of Bricanyl Turbuhaler required by each child during the study were recorded. Adverse events were documented by open questioning during each clinical visit.

Statistical analysis

Change in Bricanyl Turbuhaler inhalation technique from baseline at the beginning of the Bricanyl Turbuhaler treatment as compared to those at the end of study was assessed using the Wilcoxon signed-ranks test. Percentage of predicted normal PEF[11] was assessed as the primary measure of efficacy. Student's paired *t*-test was used to test for statistical significance of changes in PEF. For PEF recorded at each clinic visit, values from baseline at the beginning of the Turbuhaler was compared with values measured on the last clinic visit. For PEF recorded in the diaries, means over the 7 day run-in period, were used to compare with those recorded during the last 3 weeks of the treatment period. For symptom scores recorded on diary cards, means over the 7 day run-in period were compared to means over the last 3 weeks of treatment by Wilcoxon signed-ranks test. Comparison of patient's ability in achieving maximum inhalation technique scores amongst those with or without previous experience with MDIs was performed with contingency table analysis. A p value of less than 0.05 was considered statistically significant.

RESULTS

Eighty-six children were initially enrolled into the study. However, two patients were lost to the follow-ups during the first 2 weeks of the active treatment while one other patient was excluded due to violation of the protocol, thus, leaving eighty-three children with complete data available for the analysis.

Inhalation technique and acceptance

Percentage of patients correctly used Turbuhalers, in each technique category, at the beginning and at the end of the medication period, are depicted in Figure 1. Maximum scores for inhalation technique improved significantly after both written ($p < 0.001$) and verbal ($p < 0.001$) instruction following 4 weeks use of the Turbuhalers as compared to scores at the beginning of the study. Verbal instructions yielded significantly

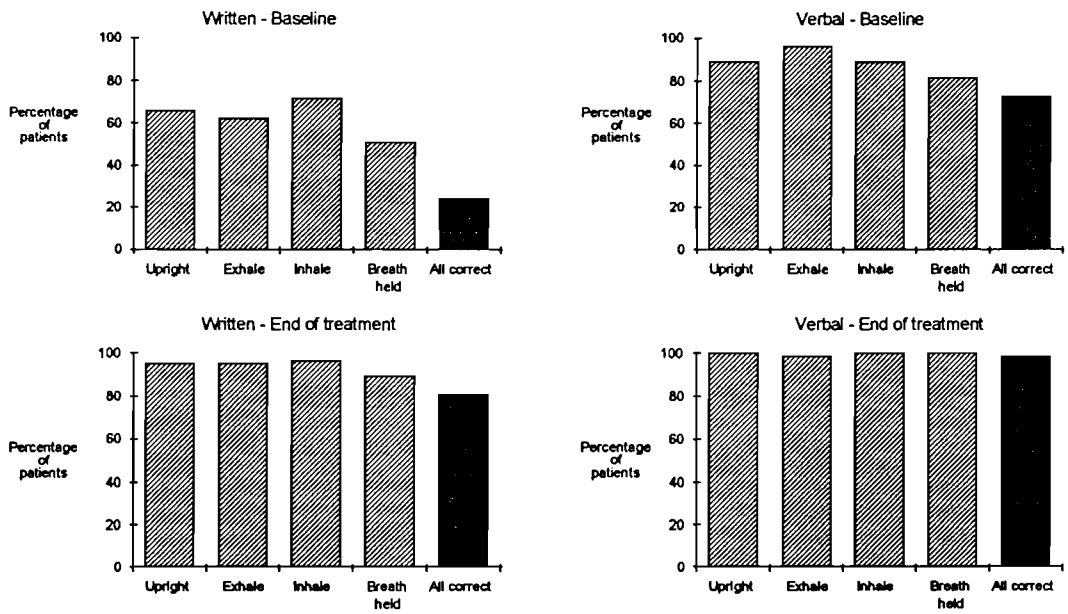

Fig. 1. Percentage of patients that correctly used Bricanyl Turbuhaler after written and verbal instruction at baseline and the end of treatment. Technique was assessed with regard to four categories (shaded bars); loading the Turbuhaler in the upright position, exhalation, inhalation, breath holding for 10 seconds. The black bars represent the percentage of patients that performed all categories correctly.

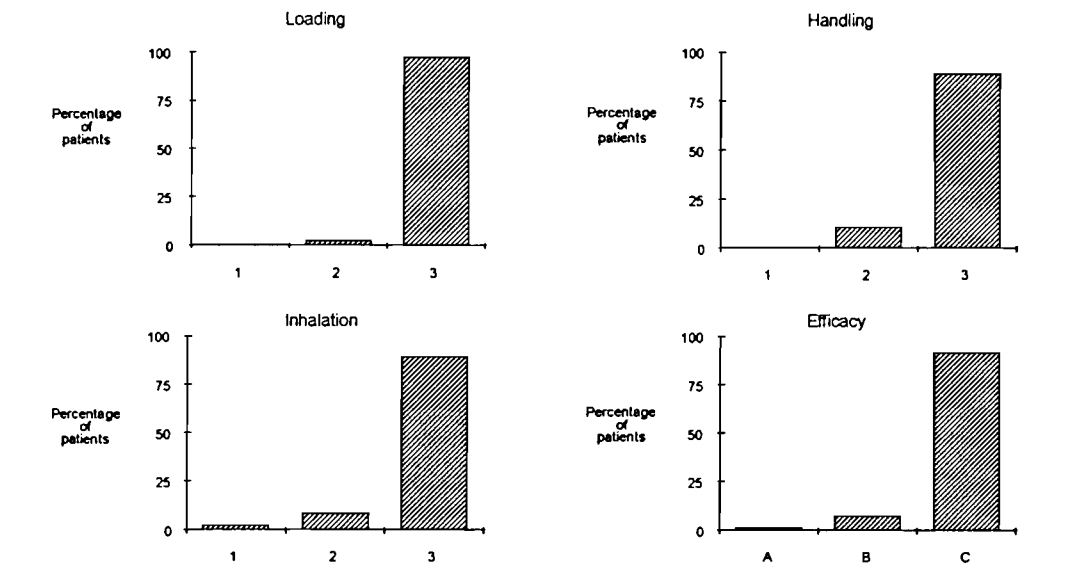

Fig. 2. Patients acceptance of Bricanyl Turbuhaler with regard to loading, handling, inhalation and efficacy. (1 = difficult, 2 = neither easy nor difficult, 3 = easy, A = ineffective, B = neither effective nor ineffective, C = effective).

Table 1. The numbers of patients with adverse events (total number = 86).

Adverse event	Number
Appendectomy	1
Cough	1
Cough, phlegm	1
Fever	1
Hand tremor	1
Headache	1
Headache, abdominal pain	1
Headache, phlegm	1
Headache, vomiting	1
Nasal congestion, cough, wheeze	1
Palpitations	1
Palpitations, nausea	1
Palpitation, sore throat	1
Rhinitis, cough, palpitations	1
Rhinorrhea, cold	1
Skin rash, cold, rhinorrhea	1
Sleep-excessive movement, nausea	1
URTI	8

better results for inhalation technique scores than written instructions at all times ($p < 0.001$). When the four categories of inhalation technique were examined individually, it was found that the part that children were having the most difficulty with, were breathholding for 10 seconds after inhalation. Acceptance of Bricanyl Turbuhaler amongst patients as ascertained by verbal questioning at the end of the study is shown in Figure 2. Ninety percent of the children considered loading, inhalation and handling of Bricanyl Turbuhaler to be easy, while 90% considered it to be effective in relieving their symptoms.

Fifty-eight of these eighty-three enrolled had used MDIs previously, the influence of this previous experience on the use of Turbuhalers was examined. At baseline after written instruction 4/26 (15%) of patients who had not and 16/57 (28%) patients who had used MDIs before achieved maximum inhalation technique scores for Turbuhaler ($p = 0.21$). After verbal instruction 15/26 (58%) and 46/57 (81%) patients who had not or had used MDIs before achieved maximum scores for inhalation technique ($p = 0.02$). After 4 weeks of treatment with Bricanyl Turbuhalers, no apparent difference in inhalation technique scores between those patients who had not or had used MDIs previously, were observed. With regard to patient acceptance, no differences in the results for the assessment of loading, inhalation, handling and efficacy by questionnaire between these two groups were observed.

Efficacy and symptom relief

Peak expiratory flow rate (PEF, expressed as mean percentage of predicted normals ± SEM) was 86 ± 3% at the first clinic visit, 99 ± 2% at baseline (at the end of the run-in period), and 104 ± 2% at the last visit following 4 weeks treatment with the Bricanyl Turbuhaler. PEF increased significantly from baseline to the end of active treatment ($p < 0.01$). Asthma symptom scores were significantly reduced following Bricanyl Turbuhaler treatment being 0.65 ± 0.07 before and 0.40 ± 0.06 after treatment during the day ($p < 0.01$) and 0.76 ± 0.08 before and 0.47 ± 0.07 after treatment during the night ($p < 0.01$) as reported at the clinic visits.

Mean (± SEM) of morning PEF values from diary cards was 93 ± 2% at baseline and was 100 ± 2% during the period of Turbuhaler treatment, with the mean increase of 8 ± 2% ($p < 0.0001$). Evening mean (± SEM) of PEF values was 97 ± 2% at baseline and was 103 ± 2% during the treatment, an increase of 6 ± 1% ($p < 0.0001$). Mean asthma symptom scores during the treatment period were significantly reduced compared to those during the baseline for both morning scores (0.45 ± 0.06 *vs* 0.32 ± 0.05; $p < 0.005$) and evening scores (0.05 ± 0.07 *vs* 0.34 ± 0.06; $p < 0.0001$).

Adverse events

The adverse events were in general mild and transient in nature as tabulated in Table 2.

DISCUSSION

Pressurized metered dose inhalers (MDIs), due to its relative ease of use, have been the mainstay of devices to administer β_2-agonists in asthma.[1,2] Nevertheless, 30% of adult patients and up to 60% of pediatric patients found MDIs to be difficult to use and are unable to use them correctly despite adequate instructions from therapists.[3] Problems commonly encountered are often related to incoordination of handling and inhalation from MDIs, particularly observed amongst young children and elderly patients.[3,5] Turbuhaler is a simple device to use and several experts felt that this device would be most suitable for children due to characteristics such as efficacy at low inhalation flow rate.[6] The device has been subjected to an evaluation in caucasian children and has been found to be both effective and acceptable to children participated.[7-9] Nevertheless, no such study in children of other ethnicities, particularly in Asian children, have been available. The results of our study demonstrated that Asian children as well as their caucasian counterparts were able to master the Turbuhaler technique at the same frequency. After combined written and verbal instruction, 73% of patients were able to achieve the maximum score of 4 and at the end of the 4 weeks active treatment 99% were able to use Turbuhaler correctly. Inhalation technique was generally poor after written instruction alone (only 24% of patients achieved the maximum score of 4, although it must be taken

into account that some of the young children could not read). Most, if not all children in our study, even pre-school children were able to correctly use the Turbuhalers after verbal instruction; these results were very similar to those performed in caucasian pre-school children.[7,8] Repeated verbal instruction about the inhalation technique has been shown to yield the best results in teaching patients how to inhale correctly.[5] Breath-holding, the least scored item in our study, were due to underestimation of time (10 seconds) by most patients. Nevertheless, after the initiation of our study, it has recently been reported that breathholding may not at all be necessary to obtain full bronchodilator benefit from Turbuhaler use[6,13] and thus more patients from our region will be able to achieve correct technique for this device.

The Turbuhaler was well accepted among our group of Asian children. Ninety percent of our children considered the Turbuhaler technique of loading, handling and inhalation to be easy to accomplish and also ninety percent were convinced that Bricanyl Turbuhaler was effective in bringing about the symptom relief. Only one child considered Bricanyl Turbuhaler to be ineffective. The reason for this could be the mild asthmatic condition that she had with no attacks occuring during the study period (no extra use of Bricanyl Turbuhaler was recorded) rendering no chance for this patient to actually feel the effect of the inhaler.

It was not surprising that patients who had previous experience with MDIs scored better with Turbuhaler than those who had not. The reason may be due to familiarity with more complicated steps involved in their previous MDI use. Nevertheless, the difference in Turbuhaler technique scores, between those with and without previously MDIs experience became inapparent at the end of the study indicating that the new device can be easily mastered within a short period of time. Moreover, patients' acceptance between the two groups were similar indicating that previous MDIs experience did not seem to be a major factor for patients to decide whether to favor the new device or not.

In this study, the terbutaline Turbuhaler did improve PEF and did reduce asthma symptom scores in our patients significantly as compared to their baseline measurements. However, due to the open experimental design used in our study with the absence of placebo or active controls, changes observed might not necessarily have been an effect of the active treatment *per se* and thus our results should be regarded as preliminary results rather than conclusive ones. However, β_2-selective agonists such as terbutaline have previously been shown to have a beneficial effect compared to a placebo in improving pulmonary function and in reduction of asthmatic symptoms.[9] Terbutaline Turbuhaler has been shown to be equipotent in relieving asthma symptoms when compared to the same dose of same drug loaded in other inhalation devices.[9,14-16] It is, therefore, possible that our preliminary data on clinical efficacy would be confirmed by a study performed in a more strict manner to clinically evaluate the device, ie in a double-blind, placebo-controlled fashion. Nevertheless, we have decided not to pursue such investigation since after completion of our study, reports indicating potential hazards of regular use of β_2-agonists have become available.[1,2] Furthermore, within these 4 weeks of terbutaline treatment in our study, we did not observe any deterioration of lung functions (rather an improvement) from regular use of Bricanyl Turbuhaler concurring with other comments that undesirable results previously reported could have been due to prolonged action of a specific drug rather than due to effects of the whole class of beta-agonists.[17]

Relatively few and minor adverse events were observed in this report with only hand tremor and palpitations that would appear to be directly attributable to β_2-agonist actions of Bricanyl Turbuhaler.[1,2] Complaints of upper respiratory tract infection symptoms such as cough, sputum, running nose, blocked-nose, sneezing and phlegm, along with headache, fever, nausea, dizziness reported in 8 patients may not have been directly associated with the use of Bricanyl Turbuhaler since this is a syndrome commonly observed amongst Asian children.

In conclusion ninety-nine percent of the childen in this study were able to achieve maximum inhalation technique scores for Turbuhaler after written and verbal instruction at the end of active treatment period. Repeated verbal instruction in the use of Turbuhaler is recommended to achieve maximum inhalation technique scores. Most Asian children in this study found terbutaline Turbuhaler to be easy to operate and effective in symptoms relief. Moreover, terbutaline Turbuhaler was found to be well accepted and should be considered a viable alternative treatment for asthma in Asian children.

REFERENCES

1. Barnes PJ, Chung KF. Questions about inhaled β_2-agonists in asthma. Trends Pharmacol Sci 1992; 13 : 20-3.
2. Lipworth BJ. Risks versus benefits of inhaled β_2-agonists in the management of asthma. Drug Safety 1992; 7 : 54-70.
3. Crompton GK. Problems patients have using pressurised aerosol inhalers. Eur J Respir Dis 1982; 63 (Suppl 119) : 101-4.
4. Wetterlin K. Turbuhaler : A new powder inhaler for the administration of drugs to airways. Pharmaceut Res 1988; 5 : 506-8.

5. King D, Earnshaw SM, Delaney JC. Pressurised aerosol inhalers : The cost of misuse. Brit J Clin Prac 1991; 45 : 48-9.

6. Hansen OR, Pedersen S. Optimal inhalation technique with terbutaline Turbuhaler. Eur Respir J 1989; 2 : 637-9.

7. Goren A, Noviski N, Springer C, Maayan CH, Godfrey S, Stahl E. The ability of young children to use a powder inhalation device (Bricanyl Turbuhaler®) efficiently. Eur respir J 1991; 4, (Suppl 14) : 277.

8. Nankani J, Follows R, Stahl E. Comparison of Terbutaline Turbohaler® and Salbutamol syrup in the treatment of wheezy children. Eur Respir J 1991; 4, (Suppl 14) : 276.

9. Lopes Dos Santos JM, Costa H, Stahl E, Wiren JE. Bricanyl® Turbuhaler® and Ventolin® Rotahaler® in exercise-induced asthma in Children. Allergy 1991; 46 : 203-5.

10. Sheffer AL, Chairman. International consensus report on the dignosis and management of asthma. Clin Exp Allergy 1992; 22, (suppl) : 1-63.

11. Lam KK, Pang SC, Allan WGL, *et al.* A Survey of Ventilatory Capacity in Chinese Subjects in Hong Kong. Ann Hum Bio 1982; 9(5) : 459-72.

12. Paterson JW, Woolcock DJ, Shenfield G. Bronchodilator drugs. Am Rev Respir Dis 1979; 129 : 1149-88.

13. Burt H, Keenan SP, Fleetham JA. Efficacy of different inhalation techniques with a breath-actuated dry powder beta-agonist inhaler. Am Rev Respir Dis 1991; 143 (No 4 Pt 2) : A 655.

14. Osterman K, Stahl E, Kallen A. Bricanyl Turbuhaler® in the treatment of asthma : a six week multi-centre study carried out in Sweden, the United Kingdom, Denmark, Norway and Finland. Eur Respir J 1991; 4 : 175-9.

15. Ahlstrom H, Svenonius E. Svensson M. Treatment of asthma in pre-school children with inhalation of terbutaline in Turbuhaler as compared with Nebuhaler. Allergy 1989; 44 : 515-8.

16. Hultquist C, Ahlstrom H, Kjellman NIM, Malmquist LA, Svenonius E, Melin S. A double-blind comparison between a new multi-dose powder inhaler (Turbuhaler) and metered dose inhaler in children with asthma. Allergy 1989; 4 : 467-70.

17. Nelson HS, Szefler SJ, Martin RJ. Regular inhaled beta-adrenergic agonists in the treatment of bronchial asthma: Beneficial or detrimental. Am Rev Respir Dis 1991; 144 : 244-50.