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The Role of Disodium Cromoglycate-Metered Dose Aerosol Inhaler in the Management of Asthma in Thai Children

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SUMMARY **Metered dose aerosol inhaler of disodium cromoglycate (Intal®) has been recently introduced to facilitate the ease of administration of the drug over its previous spincap formulation. We evaluated the efficacy of regular use of metered dose inhaler of disodium cromoglycate (DSCG-MDI) in the daily management of Thai asthmatic children. The study comprised nineteen children with the age range of 8-15 years (mean 11.6 years). During a two week baseline period, the patients recorded their baseline symptom scores, requirement of their asthma medications (medication scores) and their morning/evening peak flow (PEFR) readings. Thereafter, DSCG-MDI was prescribed at the dosage of two puffs (1 mg/puff) four times daily for eight weeks. Patients were examined at two week intervals at which daily score cards along with PEFR records were collected. Significant reduction in the medication scores and in the requirement for maintenance bronchodilators were noted ($p < 0.01$) within two weeks of use of the DSCG-MDI. Morning and evening PEFR's increased significantly and this increase reached statistical significance at 4 weeks after the initiation of the treatment ($p < 0.01$). No side effects were reported throughout the study; the aerosol was well tolerated. In this open study DSCG-MDI, at a dose of 1 mg four times daily, significantly improved asthma symptoms along with PEFR readings in Thai asthmatic children and reduced the need for concomitant asthma medications.**

Asthma, a common disease in childhood, is estimated to occur at an alarmingly high rate of 5-10% in the population of this age group.[1] In general, childhood asthma is frequently found to be associated with allergic factors.[1] At least 64% of Thai asthmatic children suffer another allergic diseases such as allergic rhinitis, urticaria, atopic dermatitis and food allergy.[2] In recent years, it has become apparent that airway inflammation contributes to the pathophysiology and the chronicity of asthma.[3] As a result, recent emphasis has shifted towards the use of antiallergic and prophylactic therapy in the long term management of asthma, particularly in children. Disodium cromoglycate (DSCG), an antiasthmatic agent, inhibits mediator release from mast cell granules[4,5] and also inhibits the activation of inflammatory cells participating in asthma process such as eosinophils and neutrophils, directly or indirectly.[6,7] With its ability to block the release of mediators of inflammation, DSCG has been shown to inhibit both immediate and late-onset asthmatic responses.[8] Its use in asthma (both short and long term) have been found to be associated with fewer asthmatic exacerbations, with a reduction in the requirement for additional asthma medication and with an improvement in lung functions.[9,10] Since lactose powder in DSCG spinhaler (the original formulation of DSCG) tends to form clumps within a short period on storage in high humidity such as occurs in South East Asia, pressurized metered dose aerosol formulation or metered dose inhaler (MDI) of DSCG (DSCG-MDI, Intal inhaler, Fisons laboratory, Loughborough, Leicester, United Kingdom) has been introduced to circumvent the problem and to facilitate the ease of its use. A recent multicenter, double blind, placebo controlled trial of DSCG-MDI has confirmed the effectiveness of DSCG in MDI formulation, at least in a group of patients who had previously res-

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ponded to DSCG spinhaler.[10] It is the purpose of this study to establish the efficacy of DSCG-MDI formulation in the daily management of asthma in Thai children.

MATERIALS AND METHODS

Patients studied were asthmatic children in the age range of 8 to 15 years, attending the Pediatric Allergy Clinic, Faculty of Medicine Siriraj Hospital, Mahidol University (Bangkok, Thailand). Their asthma condition was considered moderately severe to severe as defined by their degree of symptoms (symptoms occurring almost daily and nightly, often leading to occasional absence from school) and by the medications required to control asthma symptoms (continuous theophylline administration in addition to beta adrenergic drugs together with occasional bursts of corticosteroids). Subjects were excluded from the study if they suffered acute upper respiratory tract infections within a week prior to enrollment and if they reported hypersensitivity to DSCG use. The study was of an open design which included a two week run-in (baseline) and an eight week drug trial treatment period (Figure 1). During the run-in period, patients continued to receive their previously prescribed bronchodilators and they were required to keep diary cards on which they recorded their asthma symptom scores with the score of 0 to 5 (0 = no symptoms, 5 = severe symptoms requiring additional drugs and interference with ongoing activities such as sleep and daily activity). These symptoms were day and night-time cough, chest tightness and dyspnea. The requirements for bronchodilators and the best of three efforts of peak expiratory flow measurements using Mini-Wright's peak flow meter (Clement Clarke, London, England) both upon arising and before retiring were also recorded on the same score cards. During the eight weeks treatment period, patients were seen on a 2-week basis (4 visits) during which the following activities were carried out: complete physical examination, collection of diary score cards, distribution of supplies of trial medications and alteration of asthma management according to patients' condition. Routine pulmonary function testing measuring forced expiratory volume in one second (FEV1), forced vital capacity (FVC), the FEV1/FVC percent ratio and peak expiratory flow rate (PEFR) were performed at baseline and during each visit using a Microspiro Hi298 spirometer (Chest Corporation, Tokyo, Japan). The dose of DSCG-MDI used in this trial was 2 puffs (1 mg/puff) four times daily. Complete blood count, urinalysis, and blood chemistry were monitored at the beginning and at the end of the trial period. During the trial, the patients were asked to reduce the use of bronchodilators to the level that required to control their asthma symptoms. At each visit, patients were also queried about any unusual symptoms or signs which could have been potential adverse effects of the trial medications.

Comparisons of data (medication scores, symptom scores, peak expiratory flow results and other spirometric data) between visits were analyzed using analysis of variance (ANOVA) with repeated measures and the Wilcoxon Matched Pairs Signed Rank test.

RESULTS

Twenty children (10 males and 10 females) were enrolled, however one patient dropped out from the study by the end of the run-in period due to his inability to properly perform the peak expiratory flow rate maneuver. The age range of the remaining 19 subjects (14 extrinsic, 5 intrinsic) which formed the basis of the study, was between 8 and 15 years (mean age ± standard deviation = 11.4 ± 1.8 years). The medication and symptom scores at baseline and during the trial period are depicted in Figure 2. The scores at visit 2 represent the baseline scores recorded at the end of the run-in period. From Figure 2, it is apparent that significant reduction in both symptom scores and the requirement of asthma medications occurred after only 2 weeks use of DSCG-MDI ($p < 0.01$). The trend for continuing reduction of both scores could be observed with a maximal reduction in symptom score of 29% observed during visit #5 (6 weeks of treatment)

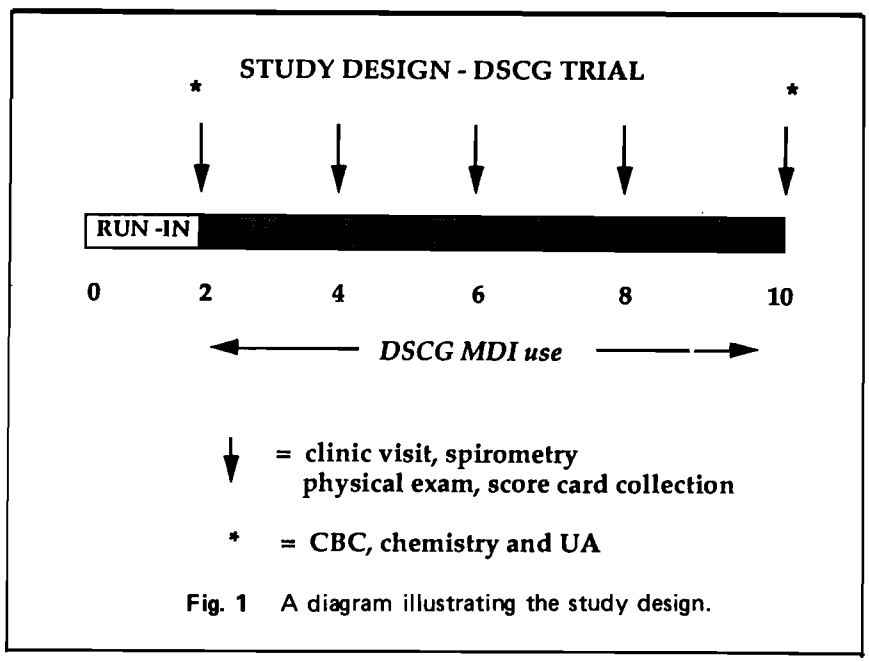

Fig. 1 A diagram illustrating the study design.

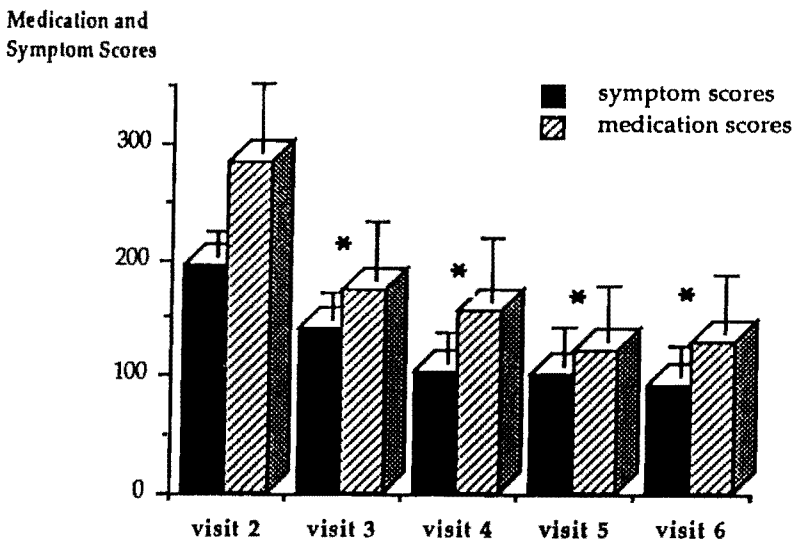

Fig. 2 Asthma Medication and Symptom Scores (multiply by 100). The reduction of asthma symptom scores (solid column) and medication scores (striped column) from the baseline reached statistical significance (*=P<0.01) after two weeks use of DSCG. This significance continued throughout the trial period.

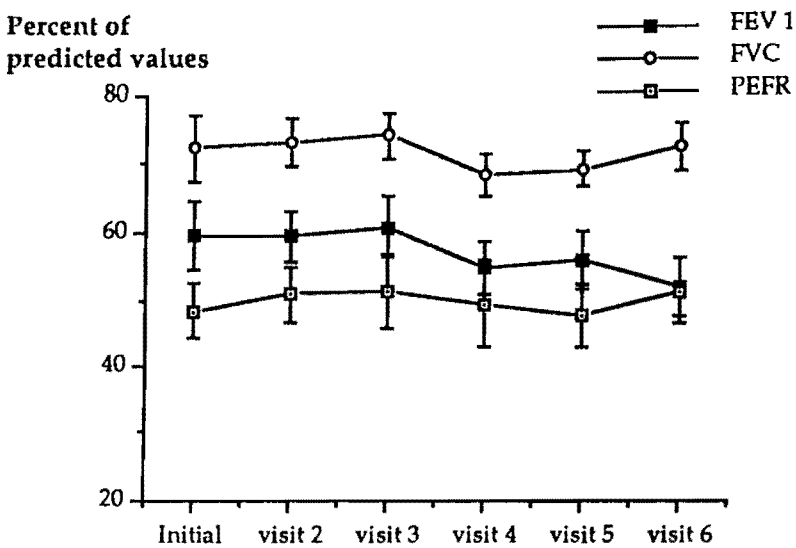

Fig. 3 Pulmonary Function Tests. Mean ± standard errors (of means) of forced expiratory volume in 1 second, forced vital capacity and peak expiratory flow rate from all patients at each visit. There was no statistical difference ($P > 0.01$) noted between mean baseline values and other interval values.

and a maximal reduction in medication score (of 59%) observed during visit #5 (after 6 weeks of treatment). Data on spirometric measurements (FEV1, FVC, PEFR) obtained at each visit demonstrated a small and insignificant variation between visits ($p > 0.05$, Figure 3) throughout the trial period. However, the results of morning and evening PEFR readings taken daily showed significant improvement despite a reduction in the requirement for other asthma medications and this improvement was observed from visit 4 (after 4 weeks of treatment) onward and throughout the rest of the treatment period. The absolute rise in morning PEFR (mean = 23.1 L/min) was greater than the rise observed for evening PEFR (mean = 18.45 L/min, Figure 4). The treatment was well tolerated by all patients. No patients withdrew from the study after the run in period and no unusual symptoms were recorded during the course of the treatment.

DISCUSSION

Although our study design was an open one, this study is the first to establish the efficacy of DSCG-MDI in the management of asthma among Thai asthmatic children. Moreover, no adverse effect of the drug was observed in this group of asthmatic children. Similarly, a previous investigation in children aged 4-13 years conducted in Israel, in a double blind cross over manner, also indicated an improvement in both lung function and in symptoms after 1-3 weeks of therapy with DSCG-MDI.[11] The effectiveness of DSCG-MDI was observed in a large multicenter trial, in the USA., involving both adults and children who had previously required DSCG in spinhaler formulation for the control of their asthma.[10] Due to the facts that (a) aerosol particles generated from MDI are smaller and can penetrate more efficiently into the peripheral airways, and (b) more mast cells are situated

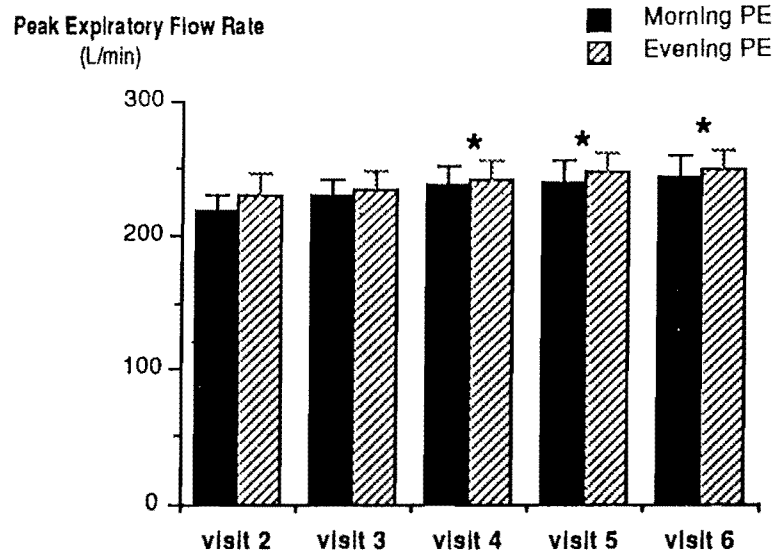

Fig. 4 Peak Expiratory Flow Rates. The improvement of both morning PEFR (solid columns) and evening PEFR (striped colums) were statistically different from the baseline after 4 weeks of DSCG use (at visit 4, * = $p < 0.01$) and maintained until the end of the study.

deep within the smaller conducting airways,[12] clinical efficacy with DSCG-MDI is expected to occur sooner than from spinhaler formulation in which particles are larger and are deposited mainly in the larger airways. This hypothesis is substantiated both in our study and by Gelle-Bernstein *et al,* [11] since the improvement on both symptom scores and the requirement of additional bronchodilators occurred rapidly after a brief 1-2 weeks of use of DSCG-MDI. Moreover, the recommended dose of DSCG-MDI (1 mg, 4 times daily) has previously been shown to be as effective as the conventional dose of DSCG-spinhaler (20 mg, 4 times daily).[13]

Our previous experience with DSCG-spinhaler[14] in Thai asthmatic children was quite similar to DSCG-MDI with the only exception being that the improvement in PEFR reached statistical significance with DSCG-MDI but not with spinhaler. This increase (with MDI) occurred despite the reduction in the requirement for asthma medications. Moreover, the increase of the morning PEFR values was greater than the increase in the evening PEFR values. As the morning values were generally lower than evening values due to the circadian variation of bronchial reactivity, the greater rise in morning PEFR reflects an improvement of the bronchial hyperresponsiveness after DSCG treatment, as has been previously documented in the past.[15,16]

DSCG has been shown to be effective in the prevention of exercise-induced asthma[17] and in the attenuation of the immediate and late asthma response after challenging with environmental/occupational pollutants such as SO_2,[18] toluene diisocyanate[19] as well as exposure to allergens.[20] The mast cell stabilizing effect of DSCG is currently believed to be mediated through an interference with the calcium influx, an enhancement in phosphorylation of the 78 kDa mast cell cytoplasmic protein as well with interference with the protein kinase-C function.[21] Most of the patients in our study responded promptly to DSCG-MDI and this could have been due to the fact that most asthma in children is of allergic type, as was the case in the study by Geller-Bernstein and Levin.[11] Nevertheless, Petty and associates[22] as well as Cordier[23] have demonstrated that DSCG was effective in adult asthmatics irrespective of their atopic status. Since childhood asthma is often associated with allergy, the role of DSCG in pure intrinsic childhood asthma is difficult to establish. However, Godfrey *et al* have demonstrated that most children with perennial asthma responded to DSCG on a long-term basis.[24]

Due to a recent interest in inflammation as a primary factor in asthma, and since DSCG has been compared favorably to theophylline in the long term management of asthma in children,[25] one has witnessed an increase in the use of DSCG in the treatment of asthma even in an early stage of the disease. This approach appears to be justifiable since the administration of DSCG is safe and is associated with fewer side effect and has a wider margin of therapeutic index. Because the main disadvantages of spinhaler formulation have been in the difficulty of administration and intolerance of its use (cough) in some patients, DSCG-MDI can be regarded as a useful adjunct to the current therapy for asthma.

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