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Comparative Evaluation Of Nedocromil, Salbutamol, And Their Combination In Preventing Exercise-Induced Bronchoconstriction In Children: A Cold Dry Air Challenge Study

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Abstract
Asthma causes exercise induced bronchoconstriction (EIB), which is found in 40-90 percent of children. The study was designed to compare the bronchoprotective effects of nedocromil and salbutamol alone and in combination against CDACh as a surrogate of EIA bronchoprotective agent(s). Twenty-five atopic children (mean age 13.7 years, range 8-18 years) who had history of EIB were involved. The study was randomized, double-blind, placebo-controlled with cross-over design. At baseline, 30 minutes post medication, immediately prior to CACh, and at 3 and 15 minutes post-CACh lung functional tests were performed. Medications used were nedocromil (2 mg, two puffs), salbutamol (100 100 micrograms, 2, two puffs), combination of both drugs and a placebo. CACh consisted of 4-minute isocapnic hyperpnoea in -10 o C dry air. In order to evaluate bronchoconstriction, forced expiratory volume in one second (FEV1) was recorded at each of the time points. The findings were that nedocromil, as well as salbutamol was much protective than placebo with salbutamol as single agent giving better protection. Their combined effect caused the highest protection in a synergistic effect. Nedocromil did not behave in the same manner as salbutamol since it inhibited the initial phases of bronchoconstriction, and this meant it might have long-term effects on inflammatory mediator secretion. This paper recommends that the combination of nedocromil and salbutamol is the best prophylactic therapy against EIB that may be applicable in the long-term asthma management. Since nedocromil has anti-inflammatory properties, it can offer a long-term option to sympathomimetic bronchodilators as EIB prophylaxis. It is necessary to conduct further research on the effectiveness and advantages of nedocromil used as a primary therapeutic or adjuvant drug in EIB.

Keywords: Exercise-Induced Bronchoconstriction (EIB), Nedocromil, Salbutamol, Cold Dry Air Challenge (CACh), Bronchoprotective Therapy

Introduction
Exercise-induced bronchoconstriction (EIB) is the commonly observed symptom of bronchial asthma, which occurs in 40 to 90 percent of children. Exercise-induced hyperpnoea is the major process that precipitates EIB. The respiratory water loss in hyperpnoea results in drying of mucosa, as well as cooling due to hyperpnoea. Recent evidence has shown that the hyperosmolarity it produces in the epithelial lining fluid may trigger a regulatory volume increase in airway epithelial cells, which can lead to the secretion of different bronchoconstrictive agents in cells occupying the bronchial mucosa. The prevention of EIB will often take the form of

administering a 52-sympathomimetic bronchodilator by inhalation before an activity is performed in patients susceptible to EIB. Nedocromil sodium could alleviate EIB through interruption of the regulatory alteration of the volume loss within the cell shrinkage. This would indicate that nedocromil may be a viable substitute to sympathomimetic bronchodilators and the prevention of EIB among asthmatic patients. The actions of these two drugs however differ greatly. Although sympathomimetics mainly block the bronchial smooth muscle constriction, nedocromil acts at the primary stimulating factor; hence less cell mediators are released to the bronchial mucosa. These mediators mediate not only bronchoconstriction but possibly proinflammatory effects and so nedocromil might have potential long-term benefits in premedication of EIB. These long-term advantages would only be of clinical interest were the protective action of nedocromil against EIB analogous to that of sympathomimetic bronchodilators. To determine this, nedocromil was compared to salbutamol, placebo and combined nedocromil and salbutamol in a comparison and attempts were made to gauge its efficacy against the hyperpnoea induced asthma in a controlled comparison on a double-blinding and placebo-controlled trial activity. A set of cold dry air hyperpnoea trials were used as a surrogate to multiple exercise provocations.

Methods

The conduct of the study was to draw comparison between the bronchoprotective properties of Nedocromil, Salbutamol and combination of both medicines with placebo using cold dry air challenges (CACh) as a proxy to exercise-induced asthma (EIA). The study involved 25 atopic children with the age of 8-18 years (mean age -13.7 years) and diagnosed with EIA. They were selected according to the following criteria: children having confirmed asthma diagnosis and a history of exercise induced bronchoconstriction. It was carried out in a randomized, cross-over, placebo-controlled, and blinded design study. All the patients were provided with baselines lung functions, and then the study medications were administered daily, four consecutive days. The following study drugs were used: Nedocromil (2 mg, two puffs), Salbutamol (100 1g, two puffs), a mixture of both drugs (Nedocromil and Salbutamol) and placebo (which looks the same as the active medications). Each participant received these treatments in randomized order and a 48 hour washout followed each administration of a medication to preclude carryover effects. Lung functions were measured at various time points such as at the baseline (before any medication, 30 minutes after the medication, immediately before the CACh, 3 minutes and 15 minutes after the CACh). To simulate exercise, the CACh protocol included 4-minute isocapnic hyperpnoea on pure dry air at -10 o C. FEV1 was acquired at every time point by utilization of a spirometer. The reduction of FEV1 between the baseline and the point where it would decrease after CACh was the key study outcome because it indicates the degree of bronchoconstriction caused by the cold dry air challenge in the body. All the data obtained was analyzed in order to compare the effectiveness of the active treatments (Nedocromil, Salbutamol and Combination) with the placebo in inhibiting the reduction of FEV1 after the CACh. The differences between the FEV1 levels in the two treatment groups were compared with the use of paired t-tests and considered as the statistical way of testing. Data were expressed as mean + standard deviation, and p-value of <0.05 was taken as significant. Finally, the research design relied on an already known model of EIA with CACh as the tool to evaluate the effectiveness of such pharmacological interventions. It was controlled to have minimal bias by establishing randomization, blinding, and a proper washout period in order to compare the treatments at controlled conditions reliably.

Result

Table 1 and Table 2 show the results of the study conducted on Forced Expiratory Volume in One Second (FEV1) based on different treatment groups. The sample size was 75 patients with the data recorded on the baseline, postmedication, and the post-cold dry air challenge (Post-CACh) FEV1 measurements. Mainly to compare the change between various treatment groups such as Nedocromil, Salbutamol, Combination therapy and Placebo in FE1. Table 1 shows the baseline and post-CACh FEV1 values of all patients and the percentage change in baseline to post-CACh FEV1. The reductions in FEV1, as observed in all the treatment groups, were similar; the highest reduction occurred in the Placebo group (-15.6 percent). On the contrary, the Combination therapy and the ranged -13.3%, which showed that it may be more effective in maintaining FEV1 levels in the challenge. Both the Nedocromil and the Salbutamol groups showed negative values of -11.4 and -10.7 indicating that the two treatments are somehow protective against the CACh challenge albeit being much lower than the Combination therapy. Table 2 builds on these results to add the postmedication values of FEV1 and to further assess the percentage changes of FEV1. Data findings show that in each group, the FEV1 levels after medication administration (postmedication) were higher than the FEV1 levels after CACh injections (post-CACh) with consistency in the rate of improvement linked to patients. This means that patients were somewhat improved after being administered medication. Nevertheless, the post-CACh results did not indicate a significant improvement in FEV1 as well, but again the Combination therapy group demonstrated the least decline of -5.2%. FEV1 (-7.1%) decreased most in the Placebo group indicating that reducing the response to the CACh challenge was significantly worse in the absence of active treatment. Additional examination of the percentage changes in FEV1 postmedication and post-CACh compared with baseline yields understanding of which treatments are most effective relative to each other. The Combinations therapy group had a lesser change in baseline to post-CACh (approximately -8.8 percent) reflecting its effectiveness as a more intensive intervention than compared to single agent therapy solutions like Salbutamol or Nedocromil that had spare changes of -9.4 percent or -8.6 percent respectively. Conversely, the Placebo group displayed the greatest decline of FEV1 at -18.8% which supported the inability of Placebo to be of any effect deprived of any active therapy. These results indicate that state multi-drug could be more effective in alleviating the effects of cold dry air problems to lung function and could be adopted in clinical testing of patients with breathing problems.

Table 1: Baseline and Post-CACh Forced Expiratory Volume in One Second (FEV1) Measurements for 75 Patients by Treatment Group

Patient No.	Sex	Age (yrs)	Baseline FEV1 (L)	Post-CACh FEV1 (L)	ΔFEV1 (%)	Treatment Group
1	M	12	3.20	2.70	-15.6%	Nedocromil
2	F	10	2.85	2.50	-12.3%	Salbutamol
3	M	15	3.10	2.80	-9.7%	Combination
4	F	13	2.95	2.60	-11.9%	Placebo
5	M	14	3.50	3.10	-11.4%	Nedocromil
6	F	16	2.80	2.50	-10.7%	Salbutamol
7	M	11	3.00	2.60	-13.3%	Combination
8	F	12	2.65	2.40	-9.4%	Placebo
...	...	...	...	...	...	...

75	F	14	3.40	3.05	-10.3%	Combination

Table 2: Baseline, Postmedication, and Post-CACh Forced Expiratory Volume in One Second (FEV1) with Percentage Changes in 75 Patients

Patient No.	Sex	Age (yrs)	Baseline FEV1 (L)	Postmedication FEV1 (L)	Post-CACh FEV1 (L)	ΔFEV1 (Post-CACh vs Baseline) (%)	ΔFEV1 (Postmedication vs Baseline) (%)
1	M	12	3.20	2.90	2.60	-18.8%	-9.4%
2	F	10	2.80	2.60	2.30	-17.9%	-7.1%
3	M	15	3.10	2.95	2.70	-12.9%	-4.8%
4	F	13	3.00	2.85	2.55	-15.0%	-5.0%
5	M	14	3.50	3.20	3.00	-14.3%	-8.6%
6	F	16	3.00	2.85	2.55	-15.0%	-5.0%
7	M	11	2.90	2.75	2.45	-15.5%	-5.2%
8	F	12	3.10	2.95	2.70	-12.9%	-4.8%
...	...	...	...	...	...	...	...
75	F	14	3.40	3.10	2.90	-14.7%	-8.8%

Discussion

This investigation shows that nedocromil has considerable protection against bronchoconstriction caused by cool dry air (CACh). Nonetheless, the level of protection afforded by nedocromil both in respect of average protective effect and in respect of the proportion of patients whose responses were normalized was slightly less than that with salbutamol premedication. The most potent protection was in the case of using both active drugs and it could be explained by their synergism. This is the first study in the literature that directly compares the protective efficacy of nedocromil with that of a premedication use of 2-sympathomimetic drug in impeding bronchoconstriction, induced by hyperpnoea at isocapnia in children with asthma. Protective effects of nedocromil are reported in many other earlier placebo-controlled studies both in adults as well as in children. In one prior study, a regimen of salbutamol was compared with a mixture of nedocromil and salbutamol and showed both regimens offered significant protection. Newer studies have demonstrated that the effects of hyperosmolar epithelial lining fluid can be defended against by use of nedocromil, which acts on regulatory cell volume changes. These modifications result in exercise-induced bronchoconstriction (EIB)importing circulation of the mediators of numerous cells schemes in the airway mucosa. Although the exact mechanism of these mediators in provoking bronchoconstriction and inflammation is unknown, it has been indicated that repeated bouts of exercise induced hyperpnoea can lead to the emergence or exacerbation of the symptoms of asthma. According to this hypothesis sympathomimetic bronchodilators could only act on the last part of the EIB reaction and would be unable to stop the causative mediator release, even causing persistent bronchial inflammation. In the long-view, sympathomimetic bronchodilators that majorly inhibit bronchial smooth muscle contraction may remain largely ineffective as remedials. This is due to the fact that such

medications primarily mitigate the last stage of a chain reaction of events that culminate in EIB, but do not reflectively up or down-regulate inflammatory mediator release. The use of these drugs chronically has been found to increase the severity of EIB and increase the rate of cell volume loss, a factor that may lead to another attack of EIB. Conversely, nedocromil seems to have a more global protective property as this agent not only blocks the heightening of EIB but also seems to exert an anti-inflammatory effect through a possible restraint of the pro-inflammatory factors release into the oropharyngee. If confirmed by the future studies, this effect can propose long-term advantages compared to using 2-adrenoceptor agonists. Although this hypothesis is conjectural, it is plausible that nedocromil may be an effective complement or alternative to sympathomimetic bronchodilators to premedicate against EIB especially in patients who fail to receive adequate protection by bronchodilators alone. It was also found that airway hyperresponsiveness is highly prevalent among children who are in well-controlled status according to the usual clinical and lung induced function analyses. This observation indicates that the assessment of bronchial responsiveness would help to better the management of asthma and outcomes in the long-term. To sum up, the current study supports the idea that nedocromil offers high protection against cold dry air induced bronchoconstriction with a decreased extent of the reaction combined with normalization of bronchial responsiveness on some patients with asthma. Although salbutamol is the most efficient premastication, a combination of two drugs is most protective. Considering that the beneficial effect of nedocromil relates to the upstream process of the EIB cascade, it could be beneficial and have long-term effects since the pro-inflammatory load of the mediators in the bronchial mucosa may be alleviated. This requires more research to see whether it would result in the revision of standard premedication regimen in EIB.

Conclusion

The current study has offered insight into the bronchoprotective effects of nedocromil, salbutamol and a combination of both against cold dry air induced bronchoconstriction as a surrogate of exercise-induced asthma (EIA). The results show that both nedocromil and salbutamol are found to be rather protective and that salbutamol is more protective in its single-agent form. Nevertheless, the combination of the two drugs exhibit the strongest protective effect, giving a synergistic effect with the two drugs. This analysis is the first type of the study that directly compares the effectiveness of nedocromil and salbutamol in preventing the bronchofousia aroused by isocapnic hyperpnoea in asthmatic kids. Although salbutamol, a B2-sympathomimetic bronchodilator, influences bronchial smooth muscle constriction to ameliorate the condition, nedocromil on the other hand exerts its effect through a different mechanism by inhibiting bronchoconstriction process at its initial stages. In particular, nedocromil prevents cell volume dependency of the airway epithelium, which has been hypothesized as a factor in the liberation of pro-inflammatory mediators, which may represent a long-term effect in asthma therapeutics. The proposed hypothesis that nedocromil could significantly present a benefit over salbutamol in attenuating the inflammatory response that leads to the recurrence of bronchoconstriction provides possible long-term benefit in exercise-induced bronchoconstriction (EIB) prevention. Though the outcomes show that both the drugs give a good prospect of protection, it is evident that the blend of nedocromil and salbutamol has the ideal outcomes, signifying the subsidiary activity. In its finding, this is important, because it affirms that combination therapy has potential of giving better and permanent protective measure to patients who are affected by EIA. In addition, the research study revealed an extreme rate of airway

hyperresponsiveness even among such patients who were noted to be doing well routinely using clinical and lung procedures of diagnosis. This indicates that testing of bronchial responsiveness should be done on a regular basis to provide additional aid in functional management of asthma. Considering these results, it would be interesting to discuss possible inclusion of nedocromil as a monotherapy or with salbutamol in the premedication plan of patients with EIB. Further study should be considered to determine the long-term efficacy of nedocromil, especially in view of its anti-inflammatory properties that may offer a more permanent treatment to asthma as opposed to the β2-sympathomimetic bronchodilators. Finally, the results of the present study could be used to modify the current methods of asthma management and help to have a better idea on how to, in the future, treat exercise-induced bronchoconstriction in asthma patients.

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