The Effect of Sodium Crompromate in the Prevention of Exercise-induced Asthma*

Yang-xin Fu, M.D.
Shi-tai Ye, M.D.
Ling-yan Xia, M.D.

SUMMARY Sodium crompromate (SCP) is an isomer of disodium cromoglycate (DSCG). The two chemicals are pharmacologically similar but with different chemical synthesis. A comparative double-blind latin square study of the preventive effect of SCP and DSCG versus a placebo aerosol was carried out on a group of nine cases of exercise-induced asthma (EIA). Compared with the placebo, both SCP and DSCG were able to prevent asthma under exercise provocation, as monitored by chest auscultation and FEV_1. There was no significant difference in the percentage fall of FEV_1 on challenge. This suggests that SCP has a similar prophylactic effect as that of DSCG on EIA.

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Exercise-induced asthma refers to acute airway obstruction after exercise. According to our data, the incidence of EIA in bronchial asthma is as high as 77 per cent. It severely influences the work, study and life activity of asthmatics. Since Jones established the exercise provocative test, there has been great progress in determining the pathogenesis of EIA as well as in preventing and treating it. $Beta_2$ agonist and DSCG are mainly used for the management of EIA.[1,2] To date, no original articles on the diagnosis and treatment of EIA have appeared in the Chinese-language literature.

Recently we established a rational exercise challenge test for asthmatics as a final confirmation of EIA. A comparative double-blind latin-square study of the preventive effect of SCP and DSCG versus a placebo aerosal was carried out to evaluate a new membrane stabiliser, sodium crompromate (SCP), invented by the Institute of Materia Medica, Chinese Academy of Medical Sciences (CAMS), for preventing EIA.[3]

MATERIAL AND METHOD

Selection of subjects

Nine asthmatics who had frequent EIA attacks, which severely influenced their work, study and other aspects of normal life, were selected. None of them had clinical features of cor pulmonale, recent respiratory infection or history of smoking. All patients had bronchial asthma as defined by the American Thoracic Society.[4] In two weeks, all of them had a fall of at least 20 per cent in FEV_1 after a 6-minute exercise period on a cyclo-ergometer with a workload sufficient to induce a pulse rate of 160 beats per minute.

Table 1 shows the general presentation of the nine cases. Table 2 shows the results of intracutaneous skin testing to inhalant allergen.

Thirty volunteers were tested simultaneously using the same procedure. None of them had cardiopulmonary disease or clinical features of the neuromuscular system; nor did any of them have a history of smoking, asthma, hay fever or eczema. After the exercise provocation, none of them showed any clinical manifestations of bronchial asthma nor a greater than 12.5 per cent fall in FEV_1.

Drugs and experimental design

Sodium crompromate (Natris isocromoglycatis) is an isomer of DSCG, the structure of which has seven substituted chrom-4-one-2-carboxylic acid derivatives.[3] The DSCG and SCP aerosols were provided by the Institute of Materia Medica of CAMS. Each metered dose released 3.5 mg of the SCP and DSCG drugs; the placebo aerosol container had the same ex-

*From the Department of Allergy, Beijing Union Hospital, Chinese Academy of Medical Sciences, Beijing, People's Republic of China.

Table 1 General presentation of nine cases of asthma

Case	Sex	Age	Duration of asthma (yrs)	Allied allergies	Family history for allergies
1	F	37	5	Allergic rhinitis	–
2	F	35	3	ditto	Asthma
3	F	28	1	ditto	–
4	F	26	11	ditto	Asthma
5	M	23	10	ditto & Atopic dermatitis	Asthma
6	F	36	7	–	–
7	M	16	12	–	Asthma
8	M	23	20	–	Asthma
9	F	18	9	Allergic rhinitis	Asthma

Table 2 Results of intracutaneous skin test to inhalent allergents correlated with allergic history

Case	Inhalant allergen	Skin test
1	House-dust	+
	Dermatophagoides farinae	+
	polyvalent moulds (group 2)	+
2	Artemisia pollen	+++
	Dermatophagoides farinae	++
3	*Dermatophagoides farinae*	+
4	House-dust	+
	Dermatophagoides farinae	+
	Artemisia pollen	+
5	House-dust	++
	Dermatophagoides farinae	+++
6	–	
7	House-dust	++
	Dermatophagoides farinae	+
	Polyvalent mould (groups 1	+++
	and 2)	+++
8	House-dust	+
	spring pollen	+
9	Cotton-filled mattress	+

ternal appearence but did not contain either drug. For each test, 10.5 mg of the aerosols were given 30 minutes prior to exercise challenge. The three different aerosols were packed and labelled A, B and C by one person. The contents were unknown to the testers. The nine patients were tested with the aerosols on three different days; the patients were divided into three groups, according to a 3*3 latin square and homogeneity.[4] Table 3 shows the arrangement and percentage fall in FEV_1 after exercise provocation. Each test was performed on each patient at the same hour on different days; the same electrical power was used for the same duration under the same environmental conditions as described above.

Table 3 Arrangement of latin square and percentage fall in FEV_1 5-15 minutes after exercise

Case	Day 1	Day 2	Day 3
1	A 57.1	B 55.9	C 9.7
2	B 33.8	C 10.6	A 17.7
3	C 0	A 10.6	B 62.3
4	B 49.5	C 43	A 53.1
5	C 20	A 37.6	B 36.5
6	A 8.9	B 14.8	C 13.1
7	C 25.5	A 38	B 40.8
8	A 5.8	B 42.5	C 28
9	B 47.2	C 20	A 0

A = SCP, B = placebo, C = DSCG. The number indicates the percentage fall in FEV_1. Exercise lasted for 6 minutes with a rest of 30-minute after medication.

The equipment and procedures for challenge and calculation

A constant dynamic regulating cyclo-ergometer and an electronic spirometer were used for clinical assessment. Twenty-four hours prior to provocation, all medications, including SCP, DSCG, antihistamine, bronchodilators and steroids, were to be avoided by the patients. Also, the patients were not to exert themselves on the days of testing. Thirty minutes before exercise, the aerosols were given separately. Each patient exercised by riding the elecric cyclo-ergometer for six minutes at the same workload. This was done at the same hour on different days and with different aerosols being administered each time. Pulmonary function and chest auscultation were monitored at the following times respectively: prior to medication, 30 minutes after medication, 2, 5, 10, 15, 20, 30, 45 and 60 minutes after exercise. To quantify the severity of EIA, the change in FEV_1 was expressed as follows:[6]

$$\%\ \text{fall in } FEV_1 = \frac{FEV_1 \text{ just before exercise} - \text{lowest } FEV_1 \text{ after exercise}}{FEV_1 \text{ just before exercise}}$$

To evaluate the effect of the drug's bronchial protectivity, the change in FEV_1 was expressed as follows:[7]

$$\%\ \text{change in } FEV_1 = \frac{FEV_1 \text{ 30 min. after medication} - FEV_1 \text{ just before medication}}{FEV_1 \text{ just before medication}}$$

If the ratio of the calculation of the formula below was over 50 per cent, it indicated that the drug was definitely protective against EIA:[6]

$$\%\ \text{protection} = \frac{\%\ \text{fall in } FEV_1 \text{ after placebo} - \%\ \text{fall in } FEV_1 \text{ after active drug}}{\%\ \text{fall in } FEV_1 \text{ after placebo}}$$

RESULTS

All patients successfully completed three tests with different premedications:

1. The percentage fall in FEV_1 is shown in Table 3. There was no significant difference with regard to the different days of the test ($p > 0.05$), but there was a significant difference in FEV_1 under exercise provocation for different individuals ($p < 0.05$) and different aerosols ($p < 0.05$) under exercise provocation.[4]

Figure 1 shows the results given by the different drugs. The percentage fall in FEV_1 with the placebo was 42.6 ± 13.8; SCP, 25.6 ± 21.3; and DSCG, 18.9 ± 12.5. DSCG showed a very significant difference compared with the placebo ($p < 0.01$), but not in comparison with SCP ($p > 0.05$). SCP showed a significant difference compared with the placebo ($p < 0.05$). Four cases who took DSCG showed a percentages of protection more than 50 per cent So did three cases using SCP. Clinical manifestations of bronchospasm lasted 15-20 minutes with the placebo; in addition, FEV_1 did not recover until 30 minutes after exercise. The results of DSCG and SCP administration were very similar: the clinical features of bronchial obstruction disappeared in 5-10 minutes and FEV_1 became normal within 15-20 minutes if there had been any significant fall.

2. Concerning bronchial protectivity, Table 4 shows that there was no difference with regard to the days, drugs and individuals 30 minutes after aerosol inhalation.

3. Typical case report: Case No. 3 (Miss Wang), a 28-year-old female member of the national handball team, complained for two years of difficulty in breathing after playing handball and running. Because she suffered from EIA very frequently, training for and participating in matches became very difficult. After premedication with DSCG and SCP in the afore-mentioned manner, she failed to develop any clinical features upon exercise challenge, whereas she still had obvious chest tightness and wheeze after inhalation of the placebo prior to exercise challenge. The change in FEV_1 following exercise after different premedication is shown in Figure 2. During regular SCP treatment, the patient showed remarkable improvement in clinical symptoms, and could do the same exercise as previously but without experiencing an EIA attack.

Table 4 Arrangement of latin square and percentage change in FEV_1 30 minutes after aerosol inhalation

Case	Day 1	Day 2	Day 3
1	A 0.8	B 2.8	C 0.4
2	B 8.9	C −5.4	A −3.1
3	C 10.9	A −1.4	B −6.3
4	B −3.6	C 5	A −4.7
5	C 9	A 26.7	B 3.9
6	A 5	B 2.9	C −5
7	C 0	A 7.1	B 1
8	A 0	B −5	C 8
9	B 7	C 16.7	A 4.8

A = SCP, B = placebo, C = DSCG. The number indicates the percentage change in FEV_1

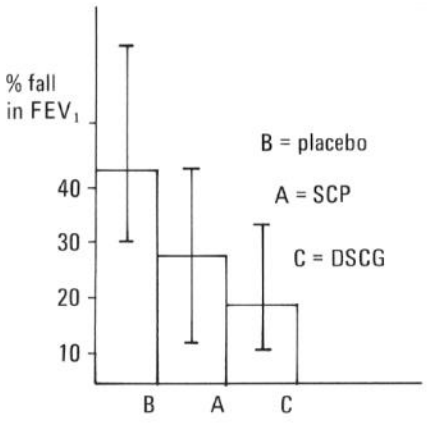

Fig. 1 Change in FEV_1 in response to exercise after inhalation of aerosols (Refer to Table 3).

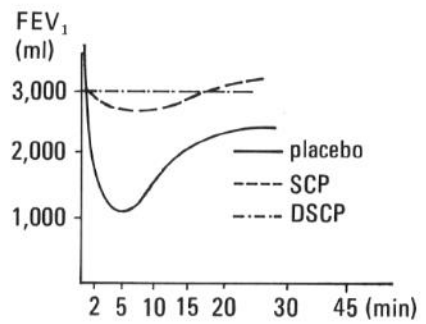

Fig. 2 The change of FEV_1 after exercise with different premedication.

DISCUSSION

Most asthmatic individuals experience acute self-limiting, sometimes severe, airway obstruction shortly after strenuous exertion or even mild physical activity. The prevention and treatment of EIA has been thoroughly investigated by allergists, chest physicians and sports medical specialists, especially in recent years.[1,2] Hyperpnoea during exercise leads to heat loss and water evaporation, which may cause transient hypertonic stimulus to bronchiole, which would affect mast cells and bronchial smooth muscle, and thus result in EIA.[8,9] During the past two decades, numerous studies have been undertaken to find the most effective agent to inhibit EIA. $Beta_2$ agonist and disodium cromoglycate are most commonly used.[1,2,9] For a patient who exercises only occasionally, an inhaled adrenergic agent might be a better preventive drug. On the other hand, people with frequent episodes of EIA cannot tolerate an overuse of $Beta_2$ agonist because of its hazardous side-effects. DSCG can be used more safely without serious untoward reaction.[9] It maintains the level of cAMP by inhibiting the activity of phosphodiesterase, regulating the calcium gate of cellular membrane and preventing mast cell degranulation. With long-term application, it may reduce some types of bronchial reflex and hyperreactivity as well.[10-12]

In long-term therapy, however, the use of bronchodilaters does not seem to reduce hyperreactivity.[10]

Because bronchial hyperreactivity correlates with the clinical severity of asthma and is the fundamental cause of asthma, it seems that the best approach to asthma control (including EIA) is prophylactic. Management with DSCG is too expensive for long-term therapy. Liang *et al* synthesised SCP as a substitute for DSCG; the procedures for SCP chemical synthesis have been reduced from seven steps to three. The technology for producing SCP has become much easier, therefore, than that for producing DSCG and output of the drug has been increased by 15 per cent,[3] which has made its price much more reasonable than that of DSCG. Experiments on animals have proven that SCP has a similar antiallergic activity in rats as compared with DSCG. Our investigation further showed that both SCP and DSCG yield no significant difference in the percentage fall of FEV_1 under the same exercise challenge. Both SCP and DSCG showed no bronchodilation effect. This suggests that SCP has an effect similar to that of DSCG in preventing EIA. The same results have been achieved in our department for antigen-induced asthma. Because there are individual differences between SCP and DSCG, it would be better to use them in accordance with the results of an exercise challenge test and the economic condition of various patients. We initially found that the subjects who responded well to the drug had a greatly reduced incidence of EIA and asthma initiated by other stimuli during long-term therapy. Certainly much more work should be carried out to determine dose-effect and time-effect relationships.

According to our statistics, the prophylactic activity of the drugs varies with individuals ($p < 0.05$). The influence of confounding factors may be avoided by self-comparison. It has been reported by different groups of investigators that the administration of a placebo may have a substantial effect on the outcome of EIA. It should be emphasised, however, that there is need for placebo control when an evaluation of a drug is made in asthmatic patients.[1,2]

It is better to use the latin square statistical method and pay attention to homogeneous distribution in order to randomise and to reduce such influences as the sequence of time, the date, and individual and drug differences, thereby greatly increasing the accuracy of statistics.

There are many methods for diagnosing asthma or bronchial hyperreaction and evaluating various therapeutic effect, but because of its natural approach, the exercise provocative test is the best method to diagnose EIA, to estimate the severity of EIA and to evaluate the efficiency of therapy in EIA.

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