Preliminary Communications

Effect of Disodium Cromoglycate on Exercise-induced Asthma

Brit. med. J., 1968, 3, 593–594

Summary: In eight patients with exercise-induced asthma, disodium cromoglycate was found to produce a definite inhibition of the post-exercise fall in forced expiratory volume in one second. This effect may be part of the cause for the subjective improvement experienced with this drug.

Introduction

Disodium cromoglycate is marketed in combination with isoprenaline as Intal Compound. It has been shown to be effective in reducing the asthmatic response to inhaled antigen (Altounyan, 1967) and to possess no bronchodilator activity and no corticosteroid type activity, nor does it antagonize the bronchoconstrictor effects of histamine, acetylcholine, or slow-acting substance (SRS-A) (Cox, 1967).

Reports have been rather conflicting in their assessment of its clinical values (Altounyan and Howell, 1967; Howell and Altounyan, 1967; Grant *et al.*, 1967; Kennedy, 1967; Smith and Devey, 1968). It would appear from the literature and from my own observations (a small double-blind controlled trial, unpublished) that the majority of patients obtain subjective improvement but that this may or may not be reflected in their forced expiratory volume in one second ($F.E.V._1$). It has, however, been of interest that several patients on Intal Compound volunteered that they had increased ability to exercise and that their asthma was less "explosive." Sudden attacks of wheeziness and shortness of breath are of course characteristic of asthma and one of its most embarrassing and distressing features, but at present it is only the resting state of asthma which is capable of easy objective measurement.

That exercise may bring on an asthmatic attack has been recognized for many years (Pearson, 1952), but the reason is still speculative (Jones *et al.*, 1963; McNeill *et al.*, 1966; Sly *et al.*, 1967b; Hafez and Crompton, 1968). During a period of eight minutes' exercise the $F.E.V._1$ may rise above or remain at the resting level, but on ceasing exercise there is a rapid marked fall which may continue for 10 to 15 minutes. The $F.E.V._1$ then returns to the resting value over the next 30 to 60 minutes (Pearson, 1952; Jones *et al.*, 1962; McNeill *et al.*, 1966). Sympathomimetic drugs can prevent the fall (Jones *et al.*, 1963; McNeill *et al.*, 1966; Heimlich *et al.*, 1966; Sly *et al.*, 1967a), while atropine (Jones *et al.*, 1963; McNeill *et al.*, 1966), antihistamine (McNeill *et al.*, 1966), and hydrocortisone (McNeill *et al.*, 1966) have no effect.

Material and Methods

Eight asthmatic patients (four males and four females) aged 17 to 47 years were studied. All had had frequent measurements of lung function tests over the previous two years, at the asthma clinic, and each case had shown marked fluctuation; changes in $F.E.V._1$ ranged from fivefold to twelvefold. All but one (Case 5) had been in hospital with status asthmaticus and responded to steroids. Routine sputum examinations showed abundance of eosinophils in all patients. All but one patient were receiving long-term steroid therapy (prednisone 5–15 mg./day; one patient was on a temporary dose of 35 mg./day). Their symptoms were under reasonable control and their steroid dosage was continued unchanged. No bronchodilator drugs were taken for 18 hours preceding each test.

Patients were at rest for 45 minutes and measurements of $F.E.V._1$ were taken at 30 and 45 minutes. The patients were then exercised for eight minutes, running up and down two flights of stairs, a total of 20 steps each 7 in. (17.5 cm.) in height. The rate of exercise was controlled so that the amount was similar in each test. Further measurements of $F.E.V._1$ were taken after three minutes of exercising, on completing the exercise, and thereafter at 3 and 10 minutes and subsequently at 10-minute intervals for a total of 50 to 60 minutes.

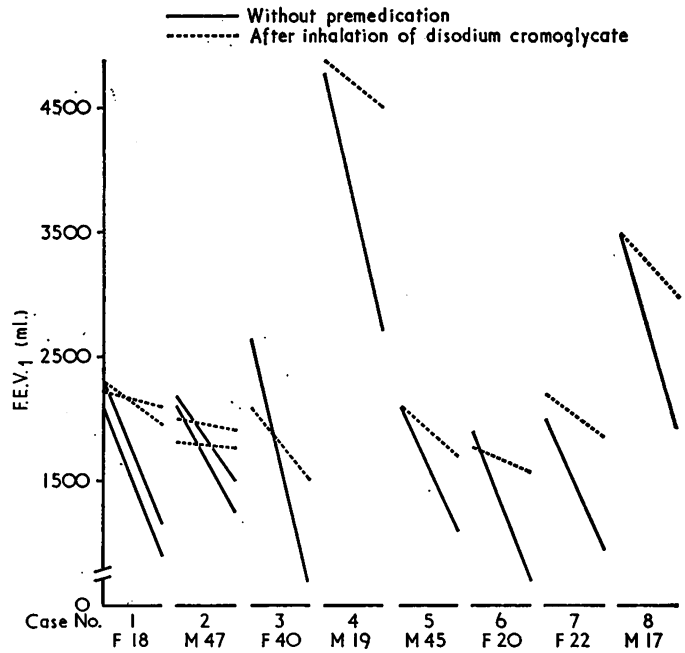

FIG. 1.—Exercise-induced asthma in eight patients; 20 tests. F.E.V.$_1$ before exercise (upper co-ordinates) to minimum F.E.V.$_1$ after exercise (lower co-ordinates).

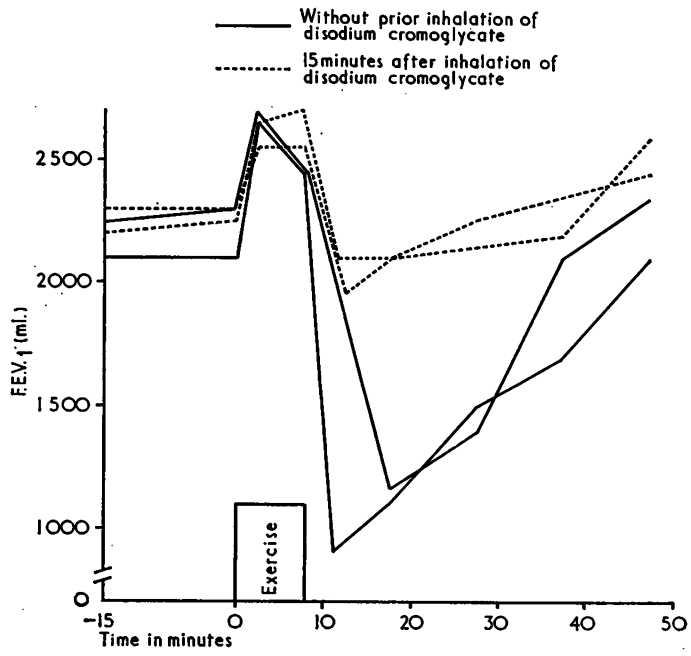

FIG. 2.—Exercise-induced asthma in Case 1.

Each patient had two exercise tests—one without medication and the other with 20 mg. of disodium cromoglycate (especially supplied without isoprenaline) inhaled 15 minutes before the exercise. In two patients the tests were repeated. Only one exercise test was carried out in a day.

RESULTS

The results obtained in the eight patients are set out in Fig. 1. The effect of exercise with and without medication on F.E.V.$_1$ is reproducible, and this is shown in Fig. 2, where the results in Case 1 are detailed.

DISCUSSION

So far only eight patients have been studied, but in each case it was found that disodium cromoglycate had a marked inhibiting effect on exercise-induced asthma, and it may well be that part of the subjective improvement recorded by patients while on this substance is due to this action.

My thanks are due to Dr. D. A. Williams for allowing me to study patients under his care and for constant encouragement; to Dr. R. E. C. Altounyan, of Fisons, for supplying isoprenaline-free Intal Compound; and to Mrs. D. N. Thomas for preparation of the manuscript.

S. E. DAVIES,* M.B., CH.B., B.SC.,
Medical Registrar, St. David's Hospital, Cardiff.

* Present address: Medical Research Council, Pneumoconiosis Research Unit, Llandough Hospital, Penarth, Glamorgan.

REFERENCES

Altounyan, R. E. C. (1967). *Acta allerg. (Kbh.)*, **22**, 487.
Altounyan, R. E. C., and Howell, J. B. L. (1967). *Proceedings of the 2nd International Symposium on Tuberculosis, Climate, Asthma, and Chronic Bronchitis.* Davos.
Cox, J. S. G. (1967). *Nature (Lond.)*, **216**, 1328.
Grant, I. W. B., Channell, S., and Drever, J. C. (1967). *Lancet*, **2**, 673.
Hafez, F. F., and Crompton, G. K. (1968). *Brit. J. Dis. Chest*, **62**, 41.
Heimlich, E. M., Strick, L., and Busser, R. J. (1966). *J. Allergy*, **37**, 103.
Howell, J. B. L., and Altounyan, R. E. C. (1967). *Lancet*, **2**, 539.
Jones, R. S., Buston, M. H., and Wharton, M. J. (1962). *Brit. J. Dis. Chest*, **56**, 78.
Jones, R. S., Wharton, M. J., and Buston, M. H. (1963). *Arch. Dis. Childh.*, **38**, 539.
Kennedy, M. C. S. (1967). *Lancet*, **2**, 838.
McNeill, R. S., Nairn, J. R., Millar, J. S., and Ingram, C. G. (1966). *Quart. J. Med.*, **35**, 55.
Pearson, R. S. B. (1952). *Acta allerg. (Kbh.)*, **5**, 310.
Sly, R. M., Heimlich, E. M., Busser, R. J., and Strick, L. (1967a). *Ann. Allergy*, **25**, 324.
Sly, R. M., Heimlich, E. M., Busser, R. J., and Strick, L. (1967b). *J. Allergy*, **40**, 93.
Smith, J. M., and Devey, G. F. (1968). *Brit. med. J.*, **2**, 340.

Hyperpyrexia During Anaesthesia

Brit. med. J., 1968, **3**, 594–595

Summary: Work in pigs has shown that malignant hyperpyrexia during anaesthesia may occur without suxamethonium having been given. A virtually constant feature in reported cases and in our own observations is that all subjects developing hyperpyrexia had received nitrous oxide and halothane.

The baffling and frightening complication of malignant hyperpyrexia occurring during anaesthesia has been described in humans by many authors (Cullen, 1966; Davies and Graves, 1966; Hogg and Renwick, 1966; Lavoie, 1966; Relton *et al.*, 1966; Thut and Davenport, 1966; Purkis *et al.*, 1967) and in anaesthetized pigs by Hall *et al.* (1966). Most of these workers attribute this unpredictable, lethal, and puzzling reaction to suxamethonium, genetically determined. We wish to report six further instances of hyperpyrexia in the anaesthetized pig. No suxamethonium was administered to these pigs as part of the anaesthetic technique. Though of the same breed and from the same farm, these pigs were not siblings. The pigs, healthy 6- to 8-week-old Landrace of 35–40 kg. weight, were being used for experimental isolated liver perfusion and liver transplantation. The anaesthetic technique, the same in each case, was as follows:

Having been starved for 16 hours preoperatively, the pigs were anaesthetized by the inhalation of nitrous oxide, oxygen, and halothane administered by means of a Magill circuit and facepiece, the animals breathing spontaneously. No premedication was given. Nitrous oxide and oxygen were administered at flow rates of 6 litres and 3 litres per minute respectively, while halothane concentration was rapidly increased to 3% during the induction of anaesthesia. As soon as the pig lost consciousness (usually within three to five minutes, depending on the size of the pig) it was removed from the portable pen in which anaesthesia was induced and placed on the operating-table. Anaesthesia was deepened for a further three to five minutes, oral endotracheal intubation then being performed (not an easy task in the pig). A stomach tube was now passed. Shortly after this, monitoring of oesophageal temperature was begun. E.C.G. and arterial and venous pressure monitoring were instituted. Anaesthesia was maintained by the inhalation of nitrous oxide and oxygen, 6 litres and 3 litres per minute respectively, with 1–2% halothane vapour administered by an intermittent positive-pressure respiration technique utilizing a non-return system powered by an East-Freeman Autovent. The minute-volume of ventilation was 8 to 9 litres. Ambient temperature of the operating-theatre varied between 15 and 20° C. during the period of these experiments.

The six instances of malignant hyperpyrexia reported here occurred in a total of 34 pigs submitted to anaesthesia. Its occurrence appeared to be quite unpredictable. In each case the rise in temperature began about the time of or shortly after the induction of anaesthesia and was heralded by a blotchy blueness of the skin. (The skin of the normal anaesthetized pig has a uniformly pink appearance.) The rise in temperature was rapidly progressive and was associated with a marked and ultimately fatal deterioration in the circulatory condition of the pig. *Pari passu* a gross metabolic and respiratory acidosis was evident. Whereas the limbs of the normal anaesthetized pig are relaxed during anaesthesia—even light anaesthesia—the limbs of the hyperpyrexial pigs were stiffly extended, the muscles in extreme spasm in a way similar to that described by Hall *et al.* (1966) in their pigs and by the Canadian workers (Cullen, 1966; Davies and Graves, 1966; Hogg and Renwick, 1966; Lavoie, 1966; Relton *et al.*, 1966; Thut and Davenport, 1966; Purkis *et al.*, 1967) in the hyperpyrexial humans following the suxamethonium they postulated as being responsible for this condition. We did not observe any marked change in pulmonary compliance. Cultures of blood taken from the first two pigs which displayed this syndrome were negative. In the last two pigs the administration of nitrous oxide and halothane was discontinued as soon as the condition became evident. From then on oxygen