Today's Drugs

With the help of expert contributors we print in this section notes on drugs in common use

Disodium Cromoglycate in Allergic Respiratory Disease

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Disodium cromoglycate is the sodium salt of 1,3-bis-(2 carboxychromon-5-yloxy)-2-hydroxypropane. The mode of action of the drug, first described and recently reviewed by Cox,[1,2] has been studied in a variety of laboratory preparations and in patients with airways disease. There are differences of detail between species, but the principal effect of cromoglycate is to inhibit the degranulation of sensitized mast cells which otherwise occurs after a challenge by antigen. The interaction of antigen with cell-bound antibody results in the release of pharmacologically active substances including histamine, 5-hydroxytryptamine, and slow-reacting substance concerned in anaphylaxis. The inhibition by cromoglycate is not specific to mast cells sensitized by heat-labile reagin (IgE) but is effective when the antibody is heat-stable IgGa and in other systems.

Cromoglycate inhibits the release of the spasmogens (apparently by stabilizing the mast cell membrane) only if it is present when the antigen-antibody combination takes place and not after the reaction has started. It does this without affecting the fixation of the reaginic antibodies to the cells or the combination of antigen with antibody. Thus it can allow hyposensitization of certain tissues while preventing the release of the pharmacological mediators of anaphylaxis.

The suggestion that cromoglycate acts as a membrane stabilizer is supported by the observation that it can also inhibit histamine release from mast cells by non-immunological stimuli—for example, the histamine-releasing substance compound 48/80,[3] human plasma, dextran, and trypsin inhibitors.[4]

Cromoglycate has no sympathomimetic, antihistamine-like, or corticosteroid-like effects. A very small proportion (less than 0·5%) of a dose of the drug is absorbed after oral administration and possibly up to 5% after inhalation of the powdered compound. When given by inhalation it has few general pharmacological effects—none that can be detected in man. The absorption, distribution, and excretion have been studied mainly in laboratory animals.[5,6] The absorbed component is rapidly eliminated unchanged in the urine and bile and no accumulation can be detected.

Toxicity

Published clinical trials have now described over 2,000 patients who have had exposure to the drug varying from a single dose to continuous use for more than two years, and no important toxic effects have been reported. Some patients have complained of irritation of the throat on inhaling the capsule, but this has occurred both with the active preparation and with the lactose vehicle. In animals no toxic effects were found in 90-day inhalation studies. The LD_{50} on parenteral administration to small laboratory animals was commonly between 2,000 and 4,000 mg/kg. In vitro tests showed that a concentration of at least 5 mg/ml was required to produce effects on the morphology of HEp2 cells and chick embryo fibroblast cells. In anaesthetized dogs, however, intravenous injection of doses of about 8 mg/kg caused immediate collapse and transient apnoea with rapid recovery; doses as small as 10 μg/kg elicited reflexes from the coronary and pulmonary circulations. These effects did not occur in other animals tested. No teratogenic effects were seen in rabbits in which the compound was given intravenously daily throughout pregnancy in doses up to 250 mg/kg.[1] There have been no reports of congenital abnormality in infants born to mothers taking cromoglycate throughout pregnancy.

Therapeutic Use

ALLERGIC BRONCHIAL ASTHMA

The earliest report[7] of the use of cromoglycate was in asthmatic patients with known sensitivity to specific allergens. For several hours after inhalation of the drug the patients were protected against asthmatic responses to inhalation of the antigen. Nevertheless, the drug is ineffective if it is inhaled even a few minutes after the antigen has been inhaled. Numerous further challenge studies have confirmed[8–16] that the drug is effective, either wholly or partially, when used prophylactically to inhibit the bronchospasm caused by inhalation of specific antigens by allergic subjects. In other words, cromoglycate may be expected to be of clinical value particularly in patients with extrinsic allergic asthma.

Intrinsic asthma has been considered to be due to hypersensitivity to some substance being produced in the body—probably in the lungs—possibly often of bacterial or other infective origin. However, the individual patient may appear to have intrinsic asthma only because it is not always possible to identify extrinsic allergens. The fact that many patients react to the high population of mites in house dust has been recognized only recently[17] and the introduction of new allergenic substances into the domestic or industrial environment[18] may pass unnoticed for a time. Investigators have demonstrated favourable responses to cromoglycate in relatively few patients with intrinsic asthma[19,20] and some [21] have found the drug to be of no value in this group of patients.

Patients with extrinsic asthma may experience prolonged periods of exposure to allergen and in those with intrinsic asthma there may be continuous or intermittent production of allergen, independent of any recent inhalation, which may continue during the course of a severe asthmatic attack. So patients with allergic asthma of either type might benefit from a prophylactic drug with the properties of cromoglycate even if it is taken after the onset of an acute attack. It is thus not necessarily logical to withhold the drug because the patient already had bronchospasm, or to withdraw it when an attack occurs despite prophylactic administration. As a practical matter, however, patients with severe airways obstruction may have difficulty in using the Spinhaler.

ALLERGIC ALVEOLITIS

Pepys *et al.*[22] discovered that cromoglycate also inhibits the delayed Arthus type reaction to some inhaled substances, including those implicated in aspergillosis and bird fancier's lung. Such late reactions may affect the alveoli only, causing allergic

alveolitis, or they may cause bronchospasm. A further complication is that the allergens (for example of *Aspergillus spp.* and of *Bacillus subtilis* used in enzyme washing powders[11,23]) may also cause immediate reactions, which are also inhibited by cromoglycate. But, in spite of the often well-defined pattern of exposure in farmer's lung and bird fancier's lung, there has been no extended clinical trial to date. Since the disease is often economically important an evaluation of cromoglycate in the individual patient seems justified.

ALLERGIC RHINITIS

Cromoglycate has been shown in three studies[24-26] to protect against nasal allergen challenge in sensitized people, though the degree of protection varied in different subjects. In clinical practice the results may be less consistent. Again there are practical difficulties of administration in patients who already have blocked nasal passages when the drug is administered.

Clinical Trials

Early controlled trials[27-30] usually showed considerable subjective benefit from the drug in terms of amelioration of symptoms, but little or no objective evidence of diminution of airways obstruction as measured by the FEV_1. It was also evident that non-allergic people[31] and patients with considerable evidence of bronchitis[30] did not benefit.

Since then numerous trials in children and in adults have confirmed that the greatest benefit is to be expected in patients with extrinsic allergic asthma.[31-40] In addition, several observers have found improvement in tests of ventilatory function or pulmonary gas exchange, or both, at rest or on exercise.[35,40-45] Improvement in objective test results may be detected when daily measurements of function are made, for example, of peak expiratory flow rate[42] when lessening of hyperinflation is sought or when measurements of specific conductance are made.

In some trials bronchitic patients have appeared to benefit if they had evidence of allergy[10,27,46,47] while others have confirmed earlier impressions that bronchitic symptoms were associated with a poor response to cromoglycate.[44] A clear definition of bronchitis was not always given in the reports of these trials.

EXERCISE ASTHMA

Exercise causes an intensification of symptoms in many patients with asthma and a few have symptoms of asthma almost exclusively related to exercise. That exercise-induced asthma can be inhibited or reduced experimentally by the prior inhalation of cromoglycate has been shown first by Davies[48] and later by several others.[13,42,49-51] Godfrey[13-52] has suggested using the inhibition of the bronchospasm induced by exercise as a method of predicting the likely clinical effectiveness of the drug. Hyperventilation can also induce asthma in susceptible patients. This may be a factor both in exercise-induced asthma and in certain types of emotional exacerbation and cromoglycate has been shown[53] to lessen the airways obstruction caused by two minutes of voluntary hyperventilation in some asthmatic patients.

Several trials have demonstrated definite corticosteroid-sparing[13,31,54-57] or bronchodilator-sparing[30,55,56] effects when cromoglycate is used, and this has been taken as one of the criteria of benefit from its use in asthma.

ALLERGIC RHINITIS

There have been six double-blind controlled trials of cromoglycate in allergic rhinitis, of which two[58,59] failed to show a statistically significant difference between drug and placebo while four[25,60-62] showed benefit from the drug. Some of the differences may have been due to variations both within the patients and in the intensity of antigen challenge during the trials. Several other uncontrolled (open) trials have reported favourably.

Administration and Indications for Use

ALLERGIC BRONCHIAL ASTHMA

The drug is available in Britain as the dry powder, of which 20 mg is contained in a gelatine capsule together with 0·1 mg isoprenaline sulphate (Intal Compound) or without the isoprenaline (Intal Spincaps). The formulation with isoprenaline is claimed to prevent the immediate bronchospasm which may occur as a result of inhaling any fine powder in some patients with hyper-reactive bronchi. A special inhaler (Spinhaler, Fisons Ltd.) is required, which contains a mechanism for puncturing the capsule, and the patient's own inspiratory effort is used to spin and vibrate the capsule in the inspired air stream. The "micronized" powder is thus inhaled into the lungs—a little, perhaps 1-2 mg, reaching the alveoli.[63] Marshall[4] has calculated on the basis of data on human bronchial morphometry that concentrations of cromoglycate which he found to be effective in *in vitro* and *in vivo* experiments on mast cell protection can be attained therapeutically in the bronchial mucosa of man.

Cromoglycate is now generally accepted to have an important place in the prevention or prophylactic amelioration of episodic bronchial obstruction in patients with allergic bronchial asthma. Some patients, particularly young ones with extrinsic asthma, respond dramatically to the drug. Most allergic patients derive a useful but more modest improvement in symptoms.

Some previously corticosteroid-dependent patients can discontinue these drugs but many require to continue taking them, though at a lower dose. As cromoglycate still appears to be of very low toxicity it seems reasonable to increase the rate of administration of the drug at times when symptoms are increasing on the probability that increased antigen challenge may be present at these times.

Where the test facilities are available the detection of inhibition of exercise-induced or hyperventilation-induced bronchospasm by cromoglycate may prove to be a useful indicator of those patients who will respond to long-term administration. Some patients derive benefit only after some weeks on the drug. Possibly this is due to hyposensitization by continued inhalation of allergen in the absence of release of pharmacological mediators of bronchospasm.[2] This mechanism is also offered as an explanation for the "carry-over" protection which may occur[38] after a period of administration of the drug.

It is essential to institute corticosteroid therapy[64] and other conventional treatment if an acute severe episode of asthma occurs or persists despite the administration of cromoglycate.

ALLERGIC RHINITIS

The manufacturers have now produced a preparation of cromoglycate for nasal insufflation (Rynacrom). Clinical trials suggest that the drug will be of value in at least some patients with seasonal allergic rhinitis.

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Any Questions?

We publish below a selection of questions and answers of general interest

Synthetic Corticotrophin in Hay Fever

Is there a place for depot tetracosactrin in the treatment of hay fever? If so, what is a safe dosage?

Most patients with pollen hay fever can be treated adequately by desensitization and with antihistamine drugs—others will respond to hydrocortisone snuff or intranasal dexamethazone in low dosage. More recently, intranasal cromoglycate (Rynacrom) has given good results.[1] Normally, treatment with a powerful drug such as corticotrophin is not indicated in as relatively trivial a condition as hay fever and I cannot find any published account of the use of depot tetracosactrin for this complaint.

However, there are some patients in whom exposure to grass pollen produces intolerable systemic and nasal symptoms which are not controlled by ordinary symptomatic remedies. For these patients it would be justifiable to try depot tetracosactrin. This drug is preferable to depot corticosteroid injections, after which hypothalamic-pituitary-adrenal function may be suppressed.[2]

Relatively high doses of depot tetracosactrin would probably be needed to give adequate control of severe symptoms, with a regime of 0·5 to 1 mg every three to five days for four to six weeks. This amount would be unlikely to produce any serious side effects,[3] though there might be temporary weight gain resulting from fat deposition and water retention.

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Treatment for Oxalate Renal Calculus

What treatment, dietary or other, might prevent a recurrence of an oxalate renal calculus in a middle-aged man with no apparent genitourinary abnormality but with a raised blood uric acid level?

The information provided is insufficient to enable the question to be answered satisfactorily. Such patients should be investigated in order to determine if a cause for their stone formation can be demonstrated. The presence of hyperuricaemia may be coincidental, associated with hyperuricaciduria, or associated with primary hyperparathyroidism. The patient should be encouraged to drink about 4 l. of fluid every 24 hours to maintain a high urinary output. If the patient is found to have idiopathic hypercalciuria, then cellulose phosphate would be the most appropriate treatment. Patients with hyperuricaciduria sometimes form predominantly calcium oxalate stones as a result of the growth of calcium oxalate on a very small core of uric acid crystals,[1] and in these circumstances treatment with allopurinol should be considered.

If careful and repeated chemical examinations fail to reveal a cause for the patient's stone, the use of magnesium oxide (or hydroxide) could be considered. This has been shown to reduce the rate of stone recurrence in primary hyperoxaluria.[2] However, I think it is very difficult to prove the effect of any line of treatment on the long term recurrence rate of urinary stones. This applies particularly to cases where there is no clear cut chemical abnormality to be corrected, as well as to the results of any dietary changes.

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