# Lithium carbonate and tetracycline interaction

Lithium is now being widely used for the long-term prophylactic treatment of recurrent affective disorders. Its many side effects have been extensively described,[1] but drug interactions with lithium have only rarely been reported. Those that have been reported[2] include interaction with diuretics, acetazolamide, aminophylline, and possibly haloperidol; an excess or decreased sodium intake may also have an effect. This paper describes a potentially serious interaction between lithium carbonate and tetracycline.

## Case report

A 30-year-old woman with a ten-year history of manic depressive illness had been attending this unit since 1974. Before that she had been admitted to hospital 11 times for mania. She never had depressive bouts. After routine tests which showed no renal impairment she was started on lithium carbonate in June 1974, and from then until April 1977 her serum lithium concentration ranged from 0·50 to 0·84 mmol/l (0·35 to 0·58 mg/100 ml). She was maintained on lithium carbonate sustained-release tablets (Priadel) 800 mg in the morning and 800 mg at night. Clinically she was quite stabilised, her mood was normothymic, and she could hold down a job. She was receiving no other medication apart from flurazepam 30 mg at night for occasional use.

On 12 May 1977, however, after developing a vaginal discharge, she was started on tetracycline 250 mg long-acting capsules (Tetrabid-Organon). She was given two tablets as a first dose followed by one tablet three times a day for seven days. Two days after she started tetracycline she had a routine serum lithium estimation, which showed a concentration of 1·7 mmol/l (1·2 mg/100 ml). This was a dramatic rise over the concentration of 0·81 mmol/l (0·56 mg/100 ml) which had been found two weeks earlier. The patient was sent for and when she appeared two days later she was slightly drowsy, with some slurring of speech and a fine tremor of both hands. She also complained of being very thirsty. Lithium and tetracycline were stopped immediately and the patient's water and electrolyte balance was maintained. Serum lithium concentration was 2·74 mmol/l (1·9 mg/100 ml) on that day and 2·75 mmol/l (1·91 mg/100 ml) the next day, but on the third day after stopping all medication the concentration fell to 1·89 mmol/l (1·3 mg/100 ml) and on the fifth day it was 0·28 mmol/l (0·19 mg/100 ml). She recovered rapidly, and there were no neurological sequelae.

## Comment

This interaction was potentially serious since the peak serum lithium concentration reached (2·75 mmol/l) was considerably above the upper therapeutic limit of 1·3 mmol/l.[1] This case therefore illustrates the danger of combining lithium with a drug that may sometimes have a nephrotoxic effect.[3] Tetracycline has been known to produce anorexia, nausea, vomiting, sodium diuresis, and polyuria in subjects who already have renal insufficiency.[4] Lithium salts in or just above the therapeutic range for treating depression may cause diabetes insipidus and negative sodium balance.[3] The fact that the tetracycline was in a sustained-release form may also have been important. There are two main lessons to be drawn from this case. Firstly, the physician should always be on his guard when lithium is combined with any drug that may affect renal function, even if, as in this case, the drug is an antibiotic. Secondly, routine serum lithium estimation has once again proved its worth, since the early stages of intoxication are often symptomless.


[1] Schou, M, Amdison, A, and Baastrup, P C, *British Journal of Hospital Medicine*, 1971, **6**, 53.
[2] Avery, G S (editor), *Drug Treatment: Principles and Practice of Clinical Pharmacology and Therapeutics*, p 940. Edinburgh and London, Churchill Livingstone, 1976.
[3] Davies, D M (editor), *Textbook of Adverse Drug Reactions*, p 182. Oxford, Oxford University Press, 1977.
[4] Meyer, L, and Herxheimer, A (editors), *Side Effects of Drugs*, vol VII, p 359. Amsterdam, Excerpta Medica, 1972.


(*Accepted 22 March 1978*)

**St John's Day Centre, Clontarf, Dublin 3, Eire**
A J McGENNIS, DPM, MRCPSYCH, psychiatrist

# SHORT REPORTS

# Oesophageal stricture: a late complication of endoscopy?

There are few recognised severe complications of upper gastrointestinal endoscopy.[1] Nevertheless, with the rapid growth of endoscopy services, these will become increasingly common and it will become more important to be aware of them.

## Case reports

*Case 1*—A 75-year-old man with chronic obstructive airways disease was initially endoscoped for the investigation of a haematemesis, when a duodenal ulcer was found. He had no other abnormality. He was transfused and treated conservatively with cimetidine and progressed well but two months later presented with dysphagia. Repeat endoscopy showed an oesophageal stricture at 35 cm. Oesophageal biopsy specimens were normal histologically. A barium meal confirmed the stricture. The stricture was dilated and three months later he was well.

*Case 2*—A 69-year-old woman underwent gastroscopy because of abdominal pain. A healing gastric ulcer was found. She was managed conservatively and the pain settled, but three months later she developed dysphagia and a repeat gastroscopy showed an oesophageal stricture at 35 cm. There was no evidence of oesophagitis and biopsy specimens were normal histologically. Barium meal confirmed the stricture. Her general condition deteriorated and she underwent laparotomy, when a pancreatic pseudocyst was found. She deteriorated and died.

*Case 3*—A 76-year-old man was initially endoscoped because of a minor haematemesis; a hiatus hernia, with minimal oesophagitis, was found. A barium meal at this time confirmed the hiatus hernia. He remained well, but three months later developed dysphagia and repeat oesophagoscopy showed an oesophageal stricture at 30 cm. On this occasion there was no evidence of oesophagitis and biopsy specimens were normal histologically. Barium meal was repeated and confirmed a tight stricture. This was dilated six times over the next two years, but he developed haemoptysis and a chest *x*-ray film showed carcinoma of the lung. He deteriorated and died.

*Case 4*—A 70-year-old woman was endoscoped because of vomiting, when pyloric stenosis and duodenal ulceration were found. She underwent partial gastrectomy and postoperatively a nasogastric tube was inserted. Two months later she developed dysphagia and a repeat gastroscopy showed an oesophageal stricture at 30 cm. Biopsy specimens were normal histologically. Because of her poor general state a Celestin tube was inserted and two months later she was reasonably well.

## Discussion

Our unit performs about 1500 gastroscopies yearly and these four patients presented over the last three years. All of them had severe oesophageal strictures which were progressive and needed active treatment. The stricture was confirmed by barium meal in all cases and only one patient had a hiatus hernia. Reflux could not be demonstrated, even on placing the patients in a head-down position. The presence of a hiatus hernia in case 3, and pyloric obstruction and later a nasogastric tube in case 4, are alternative explanations for the development of the stricture in these two cases, but no such explanation exists for the other two cases.

We think that the rapid development of a stricture so soon after a normal oesophagus had been seen at the initial endoscopy may be more than a coincidence. The pathogenesis of the stricture may be due to several factors. All our patients were elderly and this may have been an important factor. Although the initial endoscopy was performed by experienced endoscopists, who noted no difficulty at the time, it is possible, for instance, that the instrument was withdrawn in a position of fixed flexion, so causing mechanical trauma to the oesophagus, resulting later in fibrosis and stricture. An alternative explanation may be that during and after the endoscopy functional incompetence of the cardiac sphincter occurred, causing acid reflux, oesophagitis, and peptic stricture. We believe that endoscopists

should be aware that oesophageal stricture is a possible late complication of endoscopy, particularly in the elderly.

[1] Schiller, K F R, and Prout, B J, *Modern Topics in Gastrointestinal Endoscopy*, p 147-165. London, Heinemann, 1976.

(*Accepted 5 January 1978*)

**Department of Gastroenterology, Royal Victoria Hospital, Bournemouth**
G E HOLDSTOCK, MB, MRCP, medical registrar
M J WISEMAN, MB, MRCP, senior house officer
C A LOEHRY, MD, FRCP, consultant physician

# Sodium cromoglycate in intrinsic asthma

Sodium cromoglycate (SCG) gives prophylactic benefit in many patients with extrinsic asthma, but its value in intrinsic asthma, where no allergic mechanisms can be shown, is not clear.[1] Using a clinical trial we attempted to answer the following questions: (*a*) what proportion of intrinsic asthmatics respond to SCG? (*b*) over what time period does a response take place? (*c*) do responders have any identifying clinical characteristics?

## Study and results

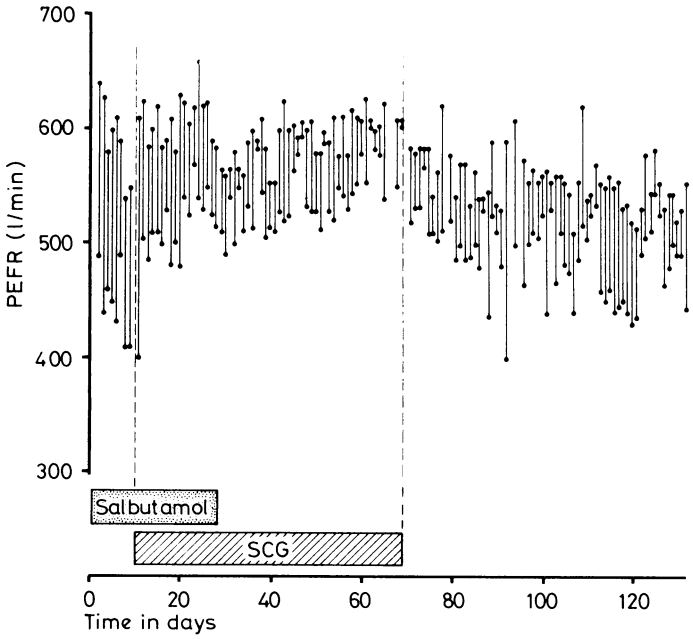
We studied 20 patients (10 of each sex), average age 57. None had a personal or family history of atopy. All had negative skin-prick tests to 18 common allergens; 10 had chronic cough with sputum. Since SCG is an inhaled powder which may cause immediate bronchoconstriction by direct irritation, a truly matching placebo cannot be prepared. Therefore lung function measurements made when the subject was taking SCG (contents of 1 capsule inhaled four times daily) were compared with control measurements, both before and after treatment. Initially, after a two-week control period, patients received SCG for four to eight weeks followed by a second control period of two weeks. Experience with the first 10 patients showed that when a response was seen it was detectable at the end of two weeks, though further response might occur over the next four weeks, and that when no response was seen in the first two weeks no response occurred subsequently. Therefore, the second 10 patients received SCG for two weeks only. Other necessary treatment for asthma, including oral prednisone 5 mg/day in four patients and beclomethasone inhalations in five, continued throughout.

Peak expiratory flow rate (PEFR) was measured as the best of three attempts with a Wright peak flow meter four times daily. The highest and lowest readings for each day were plotted as in the figure. The highest PEFRs during the last seven days of the treatment period were compared by unpaired *t* tests with the highest PEFRs of the last seven days of both control periods, with $P < 0.05$ as the level of significance. Two similar comparisons were made for the lowest PEFRs, making four comparisons for each patient. Forced expiratory volumes (using a dry spirometer), absolute lung volumes, and airways resistance (using a body plethysmograph) were measured at the end of treatment and both control periods.

Three patients showed a significant beneficial response for all four comparisons (figure). The significance levels achieved were always greater for the lowest as opposed to the highest PEFRs. Three patients showed a significant deterioration in PEFRs (and symptoms) requiring termination of the trial. The remaining 14 showed no significant change. The three patients responding positively were not detected by the infrequent comprehensive lung function testing. Although all three responders had a relatively short history of asthma (< 1 year) and had not received treatment with corticosteroids, four other patients with both these criteria failed to respond. We examined also the blood eosinophil counts, immunoglobulin concentrations, presence of autoantibodies, and degree of lung hyperinflation for prognostic significance without success.

## Conclusions

We draw five conclusions from this study. Firstly, only three of 20 patients with intrinsic asthma showed benefit from SCG, and three got worse, presumably from the direct irritant effect. Secondly, two weeks is an adequate trial period. Thirdly, we could find no clinical features which predicted a positive or negative response. Fourthly, the true effect of this mast-cell stabiliser cannot be assessed with this preparation, for there may have been patients who responded but in whom the benefit was cancelled by direct irritant bronchoconstriction. Fifthly, infrequent (even if comprehensive) lung function testing is useless in detecting drug response over days or weeks in asthmatic patients. Frequent simple measurements such as PEFR are essential.




A beneficial response to SCG. Each pair of points represents highest and lowest PEFRs on a given day. Improvement is seen mainly in the lowest readings and appears to occur progressively over two months. Salbutamol could be discontinued.

[1] Rawlins, M D, *British Medical Journal*, 1977, **2**, 701.

(*Accepted 20 January 1978*)

**Departments of Medicine and Immunology, The Middlesex Hospital Medical School, London W1**
KENNETH B SAUNDERS, MD, MRCP, senior lecturer
MICHAEL RUDOLF, MB, MRCP, Jules Thorn research fellow
JONATHAN BROSTOFF, MB, MRCP, senior lecturer

# Associated clinical syndromes in a patient homozygous for HLA B27

Several diseases are associated with the expression of certain HLA antigens,[1] the strongest being that between ankylosing spondylitis and HLA B27. About 90% of the patients with this disease possess the B27 antigen compared with only 6% of the general population.[2 3] Other syndromes associated with HLA B27 include Reiter's disease, anterior uveitis, Still's disease, psoriatic arthropathy, and various reactive arthropathies such as salmonella and Yersinia arthropathy. The clinical features of these syndromes show considerable overlap but the pathological mechanisms remain a puzzle. We report a patient who presented with features of several of these syndromes concurrently. Tissue typing revealed the expression of HLA A2, B27, and a subsequent family study suggested that the patient was homozygous at the HLA A and B loci, but not at the D locus.

## Case report

A 64-year-old man was referred to the medical clinic because of progressive stiffening and pain in the joints of his hands together with increasing low back pain developing over several months. He had also noted a persistent dry cough, urinary frequency, and dysuria. Six weeks before referral he had