Systemic mastocytosis: control of lifelong diarrhea by ingested disodium cromoglycate

J. Dolovich,* M.D., F.R.C.P.[C], N. D. Punthakee, M.B., B.SC., A. B. MacMillan, M.D., F.R.C.P.[C] and G. J. Osbaldeston, M.D., *Hamilton, Ont.*

Summary: A 16-year-old boy with systemic mastocytosis from birth had a lifelong history of pronounced diarrhea. Treatment with ingested disodium cromoglycate (DSCG) restored a normal bowel movement pattern and this has been maintained for the six months he has been on treatment. Changes in dosage have repeatedly demonstrated a close relationship between the dose of ingested DSCG and the control of the diarrhea. This case report indicates the potential efficacy of ingested DSCG in the treatment of some gastrointestinal disorders.

Résumé: *Mastocytose générale: enrayement d'une diarrhée chronique par ingestion de cromoglycate disodique*

Un garçon de 16 ans, atteint depuis sa naissance d'une mastocytose générale, souffrait depuis lors d'une diarrhée sévère. Une médication per os à base de cromoglycate disodique a permis de rétablir un transit intestinal normal et cette amélioration s'est maintenue durant toute la période du traitement. Des modifications délibérées de la posologie ont montré qu'une relation étroite existait entre la dose ingérée et l'arrêt de la diarrhée. Ce rapport clinique indique que cette substance possède une efficacité potentielle dans le traitement de certains troubles digestifs.

Disodium cromoglycate (DSCG) therapy is an important advance in the treatment of asthma.[1-5] The inhalation of DSCG inhibits asthmatic responses to a variety of stimuli including allergens[6] and exercise,[7] but it is ineffective when given by mouth since it is only minimally absorbed from the gastrointestinal tract. There is now evidence that the local administration of DSCG is also helpful in allergic rhinitis[8,9] and vernal conjunctivitis.[10] Ingested DSCG appears to prevent the intestinal reactions of food allergy.[11]

DSCG is considered to act by inhibiting the release of mediators of the allergic reaction.[1,12,13] In the presence of DSCG the interaction of antigen with membrane-bound antibodies of the IgE class is unaffected, but this interaction fails to stimulate secretion of mediators from mast cells. Since DSCG inhibits this mast cell function, and since ingested DSCG prevents intestinal reactions of food allergy, it seemed possible to us that ingested DSCG would inhibit the persistent diarrhea of systemic mastocytosis.

Case report

The subject is a white boy, born November 27, 1957 weighing 7 lb 4 oz. During approximately five months of the pregnancy an antinauseant containing dicyclomine hydrochloride, doxylamine succinate and pyridoxine had been used. A progestational hormone had been injected in treatment of threatened abortion in the third month of pregnancy. A severe case of "flu" occurred two months prior to delivery.

At the time of birth the boy had an enlarged liver and spleen and a generalized pruritic erythematous maculopapular rash. Generalized mast cell disease was diagnosed clinically. Poor feeding, vomiting and diarrhea were also present.

At age 1 year his weight was only 11 lb. A skin biopsy then showed collections of mast cells in subcutaneous tissue; the pathologic diagnosis was urticaria pigmentosa. A bone marrow examination yielded normal findings. Also normal were hemoglobin level, leukocyte count and differential, clotting time, prothrombin time, serum protein electrophoresis results and urinary serotonin assay results.

Developmental milestones were late. He sat at age 3 and began to talk after age 4. With exertion the face and, to a lesser extent, the rest of the body appeared flushed and swollen. The diarrhea persisted. At age 4 treatment with oral prednisone 5 mg *qid* was started. The liver decreased in size from 7.5 cm below the costal margin to 4.5 cm below within two weeks. The diarrhea and skin rash greatly improved but the height and weight remained static. In an effort to induce growth a total of six injections of testosterone 100 mg were administered in 1963. After two pathologic fractures of the upper extremities and a life-threatening attack of chickenpox the adrenal steroid treatment was discontinued at age 6. This was followed by rapid increase in height and weight. Diarrhea remained troublesome.

By age 10 the boy's abdomen was more protuberant and his extremities were wasted. Diarrhea was still present and continued up to age 16. The stools were liquid, pale and frothy and floated on water. There were bowel movements four to six times each day in addition to two to three times every night. Bowel sounds were loud and abdominal distension and cramps were frequent. His appetite was described as huge. Exertion caused his face to become flushed and swollen.

Physical examination at age 16 revealed numerous pale brown macular lesions of the skin. There were distinct flares on stroking. His height was 137.5 cm and weight 34 kg. The bulbar conjunctivae were injected and edematous. Mild exophthalmos was present. Extremities were wasted and the abdomen was protuberant. The spleen and liver both measured 30 cm from the upper level of dullness to the lower palpable margin. There was a trace of pubic hair and a slight thickening deep to the nipples and areola. There was no clubbing of the extremities.

Findings on chest radiography were normal. Abdominal films showed splenomegaly, hepatomegaly and increased density of the lumbar spine. Hemoglobin level was 11.0 g, hematocrit 33%, leukocyte count 3700/mm^3 (neutrophils 63%, lymphocytes 28%, monocytes 6%, eosinophils 3%), absolute eosinophil count 111/mm^3, reticulocytes 1.2% and platelets 198,000/mm^3. There were no mast cells or unusual basophils in the peripheral blood. Erythrocyte sedimentation rate was 50 mm/hr. Levels of serum albumin, total protein, calcium, inorganic phosphorus, glucose, BUN, uric acid, creatinine, bilirubin, alkaline phosphatase and SGOT were normal. Urinalysis results and prothrombin time were normal.

In September 1973 the subject was started on DSCG. Four times a day the contents of two 20-mg capsules were dissolved in distilled water and immediately ingested. During the first week there was a decrease in bowel movements and the occasional formed stool. Two weeks after the onset of treatment bowel movements were regular, three per day and formed. Nocturnal bowel movements ceased. Cramps were no longer present. There was a dramatic decrease in appetite. It was noted that occasionally, perhaps once a month, bowel movements were loose. It then became a practice to ingest the con-

From the departments of pediatrics and family practice, St. Joseph's Hospital and McMaster University, Hamilton

*Dr. Dolovich is in receipt of a grant from the Medical Research Council of Canada (MA3404) and a Queen Elizabeth II Scientist Award.

Reprint requests to: Dr. J. Dolovich, McMaster Pediatric Unit, St. Joseph's Hospital, Hamilton, Ont. L8N 1Y4

tents of three DSCG capsules for three doses and two capsules for the remaining dose, and diarrhea invariably subsided by evening. On three occasions when bowel movements were regular and formed the dose was decreased to one capsule *qid*. Each time, there was a return of diarrhea by the same evening and the dosage of two capsules *qid* was then restored.

Discussion

The excessive appetite and description of the stool suggested malabsorption; this is a reported complication of systemic mastocytosis.[14] However, in the present case direct tests of malabsorption were not performed before the onset of DSCG therapy, so that this point was not confirmed.

There was persistent diarrhea from the time of birth with some reprieve for two years, beginning at age 4, when he was taking prednisone. For 10 years the diarrhea was uninterrupted and an imposition on the way of life of the boy and his family. In recent years only antihistamine preparations have been used to treat the symptoms of mastocytosis, specifically to reduce itchiness of the skin which occurs especially after exertion. It is believed that antihistamine treatment was useful for the cutaneous symptoms but not for the diarrhea. The diarrhea was unrelenting in our patient prior to the use of ingested DSCG and subsided promptly after the onset of therapy. Changes in DSCG dosage have repeatedly demonstrated a direct relationship between the control of the diarrhea and the amount used. The evidence is strong that the cessation of the diarrhea was due to the ingestion of DSCG.

It is considered that a favourable therapeutic response from ingested DSCG would require that: (a) the chronic diarrhea be indeed a manifestation of systemic mastocytosis; (b) the diarrhea be induced by products of the mast cells and not merely mechanical effects of large numbers of these cells in the mucosa; (c) ingested DSCG have sufficient access to mast cells of the intestinal tract; and (d) functions of the mast cells in systemic mastocytosis be inhibited by DSCG. The observed results of treatment with ingested DSCG suggest that these conditions have been fulfilled.

The authors are grateful to the parents for their cooperation; to Dr. Robert Watters, medical director of Fisons (Canada) Limited for his encouragement and for a supply of DSCG (Intal®); and to Mrs. Teresa Tomlinson for secretarial assistance in the preparation of the manuscript.

References

1. Cox JSG: Disodium cromoglycate (FPL 670) ('Intal'®); a specific inhibitor of reaginic antibody-antigen mechanisms. *Nature* 216: 1328, 1967
2. Altounyan REC, Howell JBL: Treatment of asthma with disodium cromoglycate (FPL 670, 'Intal'). *Respiration* 26: suppl 131: 1969
3. Smith JM, Devey GF: Clinical trial of disodium cromoglycate in treatment of asthma in children. *Br Med J* II: 340, 1968
4. Moran F, Bankier JDH, Boyd G: Disodium cromoglycate in the treatment of allergic bronchial asthma. *Lancet* II: 137, 1968
5. Bernstein IL, Siegel SC, Brandon ML, et al: A controlled study of cromolyn sodium sponsored by the Drug Committee of the American Academy of Allergy. *J Allergy Clin Immunol* 50: 235, 1972
6. Pepys J, Hargreave FE, Chan M, et al: Inhibitory effects of disodium cromoglycate on allergen-inhalation tests. *Lancet* II: 134, 1968
7. Davies SE: Effect of disodium cromoglycate on exercise induced asthma. *Br Med J* III: 593, 1968
8. Blair H, Herbert RL: The use of disodium cromoglycate in seasonal rhinitis. *Practitioner* 208: 671, 1972
9. Engstrom I: The effect of disodium cromoglycate on nasal provocation tests in children with seasonal allergic rhinitis. *Acta Allergol (Kbh)* 26: 101, 1971
10. Easty DL, Rice NSC, Jones BR: Clinical trial of topical disodium cromoglycate in vernal kereto-conjunctivitis. *Clin Allergy* 2: 99, 1972
11. Freier S, Berger H: Disodium cromoglycate in gastrointestinal protein intolerance. *Lancet* I: 913, 1973
12. Greaves MW: The effect of disodium cromoglycate and other inhibitors on *in vitro* anaphylactic histamine release from guinea pig basophil leucocytes. *Int Arch Allergy Appl Immunol* 36: 497, 1969
13. Sheard P, Blair AMJN: Disodium cromoglycate: activity in three *in vitro* models of the immediate hypersensitivity reaction in lung. *Int Arch Allergy Appl Immunol* 38: 217, 1970
14. Broitman SA, McCray RS, May JC, et al: Mastocytosis and intestinal malabsorption. *Am J Med* 48: 382, 1970

Oral amoxicillin in acute uncomplicated gonorrhea

L. Bayne, M.B., B.S., D. Tamblyn, M.D., J. Ruedy, M.D. and R. I. Ogilvie, M.D., *Montreal*

Summary: Of 53 patients with acute uncomplicated gonorrhea treated with amoxicillin 2 g and probenecid 1 g orally as a single administration, six failed to return for follow-up examination, 10 developed postgonococcal urethritis and one was a treatment failure. The remainder achieved symptomatic cure in an average of 2.3 days. Adverse drug effects were infrequent, mild and transient. We conclude that this dose of amoxicillin and probenecid is a safe and effective treatment regimen.

Résumé: *L'amoxicilline orale dans la blennorragie aiguë sans complication*

Des 53 malades souffrant de blennorragie aiguë non compliquée et qui avaient été traités par une seule dose orale de 2 g d'amoxicilline et de 1 g de probénécide, six ne se sont pas représentés pour un examen de contrôle, 10 ont présenté une urétrite postgonococcique et un était un véritable échec thérapeutique. Les autres ont été guéris, du point de vue symptômatique, en un laps de temps moyen de 2.3 jours. Les réactions médicamenteuses défavorables ont été rares, bénignes et transitoires. Nous nous permettons de conclure que cette dose d'amoxicilline et de probénécide constitue une médication efficace et sans danger.

Amoxicillin (α-amino-p-hydroxylbenzyl penicillin) is a new semisynthetic penicillin similar in structure and in spectrum of activity to ampicillin. Both antibiotics exhibit a low degree of plasma protein binding (17 to 18%) and both depend upon renal excretion for elimination of significant portions of a dose.[1] Probenecid administration results in higher and more prolonged serum concentrations of both ampicillin and amoxicillin.[2] In comparison with ampicillin, amoxicillin is absorbed at a faster rate and more completely from the gastrointestinal tract, yielding a peak serum concentration approximately twice that for ampicillin in an equal dose.[2-5] Because of the similar minimum inhibitory concentrations (MIC) of ampicillin and amoxicillin against *Neisseria gonorrhoeae in vitro*,[2] amoxicillin might be expected to have efficacy in clinical infections of an order similar to that observed with higher doses of ampicillin.

This study was designed to test the efficacy of a single oral dose of amoxicillin with probenecid in the treatment of patients with acute uncomplicated gonorrhea.

Methods

Patients presenting to the emergency department of The Montreal General Hospital in 1973 with a history sug-

From the clinical pharmacology division of The Montreal General Hospital, and departments of medicine, pharmacology and therapeutics, McGill University

Reprint requests to: Dr. R. I. Ogilvie, Clinical Pharmacology Division, The Montreal General Hospital, 1650 Cedar Ave., Montreal, Que. H3G 1A4