THE VALUE OF AN ORAL HYPOGLYCAEMIC AGENT IN THE TREATMENT OF THE POST-GASTRECTOMY DUMPING SYNDROME

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INTRODUCTION

The difficulties in the management of the dumping syndrome by conventional medical measures have prompted a more empiric approach to the abnormalities of glucose tolerance so frequently found in this condition.

Since alimentary hyperglycaemia occurs in most of these patients, it seemed reasonable to try the effect of oral hypoglycaemic agents in its control. We elected to use chlorpropamide because of its prolonged action after single-dose administration.

MATERIAL AND METHODS

Four male patients with severe postprandial dumping symptoms were selected for this study. A Polya gastrectomy without vagotomy had been carried out for chronic duodenal ulceration in each case. Early dumping occurred in two patients, symptoms manifesting in the first 30 minutes postprandially, and one presented with the 'late' or 'hypoglycaemic' syndrome. The remaining patient, in whom symptoms appeared 60 minutes after eating, was classified as intermediate.

A three-hour oral glucose-tolerance test, utilizing 50 G. of glucose, was carried out in each patient before the administration of an oral hypoglycaemic agent. Blood-sugar estimations[1] were carried out on samples of capillary blood (finger-prick) at 10 - 15 minute intervals. Careful note was taken of dumping symptoms during the time of this and subsequent tests.

An intravenous (i.v.) tolbutamide test (0·5 G.) was carried out on the second day. Blood-sugar levels were determined at 10-minute intervals for 60 minutes.

The patients were then instructed to take one tablet (250 mg.) of chlorpropamide daily, and an unrestricted carbohydrate intake was advocated. Symptoms before and after administration of the drug were compared at weekly follow-up visits. In three patients the glucose-tolerance test was repeated after two weeks of therapy. The fourth did not return for subsequent testing.

Serum insulin-like activity was determined by the rat epididymal-fat-pad technique[2] on the fasting, 20-, 30- or 60-minute blood samples during the glucose-tolerance tests, and at 0-, 20-, 30- or 60-minute intervals after i.v. tolbutamide. The serum osmolarity and electrolytes were measured by the Fiske osmometer and flame photometry, respectively, in two patients in the fasting state, at the height of 'dumping' symptoms reproduced by the glucose-tolerance test, and at the two-hour period.

CASE REPORTS

Case 1

A.C., aged 43 years, developed moderately severe dumping symptoms six months after a ⅗ths Polya gastrectomy for chronic penetrating duodenal ulceration, carried out in July 1959. A Hofmeister valve was constructed at the time of operation. He improved slightly on a combination of anticholinergic and antacid therapy for a few months, but returned in February 1961 with severe and incapacitating symptoms.

He experienced *blurring of vision*, faintness, jitteriness, tremor, anxiety, sweating and flushing 20 - 30 minutes postprandially. He was afraid to drive his car and unable to concentrate at work. Lying down after a meal afforded some relief. He thought these symptoms were worse than his preoperative ulcer dyspepsia. He had lost 30 lb. in weight since his gastrectomy. Barium studies, the serum proteins, calcium, phosphorus and alkaline phosphatase, and the blood count were normal. An augmented histamine test showed achlorhydria. Although many of the symptoms remitted after continuous tranquillizer and anticholinergic therapy, he was still unable to think clearly or concentrate after a meal.

In July 1962 his job was jeopardized by frequent sick leave and inability to carry out his work in an orderly fashion. All the symptoms recurred with increased severity. A low-carbohydrate diet was prescribed with marked but incomplete recovery. At this stage carbohydrates were reinstituted, and chlorpropamide, 1 tablet daily, was given. One week later he had returned to work, could do arithmetical calculation after meals without difficulty, and had lost all his dumping symptoms apart from occasional blurring of vision half an hour after a meal. Therapy was maintained for four months without recurrence of symptoms, and 'he felt better than at any time since gastrectomy'.

A partial recurrence of symptoms two months after stopping chlorpropamide was again cured by the reinstitution of therapy for two weeks. At present he is maintained on a low-carbohydrate diet, 'antrenyl' and 'dianabol'. The results of the glucose-tolerance and tolbutamide tests are shown in Fig. 1.

Case 2

J.H., aged 35 years, had an anterior Polya gastrectomy in September 1960 for duodenal ulcer dyspepsia of 10 years' duration. Since discharge from hospital he had experienced late postprandial dumping symptoms between 2 and 4 hours after a meal.

Lightheadedness, tremor, jitteriness and sweating were the predominant symptoms. In addition, he was afraid to drive, could not concentrate at work and became unsteady in his gait. Although some relief was evident on lying down, this was rarely convenient or practicable. 'Probanthine' produced a partial remission in symptoms, and the symptoms tended to disappear after a meal.

He was first seen at the Gastro-intestinal Service in March 1962 and complained that his symptoms prevented him from working. Thorough interrogation did not reveal any overt psychoneurotic manifestations. His blood count, serum biochemistry and barium meal were normal, and his maximal acid output was 1·5 mEq./hr. Carbohydrate restriction and anticholinergic therapy produced a moderate improvement in his symptoms, but his weight fell by 16 lb. by the end of the first month on this regime. This prompted a trial of chlorpropamide, 250 mg. daily, with unlimited carbohydrate intake. Apart from slight lightheadedness, his previous incapacitating symptoms disappeared. However, after two weeks he felt that 'it was not helping as much as it did initially', and preferred to omit bread and sugar from his diet. A combination of chlorpropamide and probanthine, coupled with bread and sugar restriction, produced a complete remission.

At present chlorpropamide has been discontinued and he is symptom-free on moderate carbohydrate restriction, pro-

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banthine, and fluid restriction at meal times.

The results of the glucose-tolerance and tolbutamide tests are shown in Fig 1.

Case 3

G.K., a 42-year-old university lecturer, had a Polya gastrectomy with a Hofmeister valve in June 1957. A history of excessive alcohol intake antedated his gastrectomy by many years. Three weeks after operation he developed bile vomiting, unrelated to meals, which occurred once a week initially, but latterly once a month.

He was first seen at the Gastro-intestinal Service in August 1961, complaining of monthly fairly copious biliary vomiting, loss of weight, listlessness, intermittent frothy diarrhoea and periodic pyrexia. The pyrexia was attributed to afferent-loop stasis with bacterial contamination; it did, in fact, improve on antibiotic therapy. In addition dumping symptoms 50 - 60 minutes after a meal had become manifest. These comprised sweating, dryness of the mouth, unsteadiness in gait with a tendency to fall to the left, fatigue and loss of concentration and memory. This had severely affected his lecturing capabilities and he became concerned about losing his job. His blood count, serum biochemistry, and serum vitamin-B_{12} and $^{60}CoB_{12}$ uptake were all normal. The lowest pH of the gastric contents after maximal histamine stimulation was 4. The radiotriolein and chemical faecal fat estimations were normal during a period of relative constipation. The barium meal showed a partially filled afferent loop.

At this stage it appeared that many of his symptoms were psychogenic, and a combination of carbohydrate restriction, and anti-emetic and tranquillizer therapy was instituted with only slight improvement. A high-carbohydrate diet aggravated the dumping symptoms, but these appeared to be controlled by the addition of chlorpropamide. His concentration and memory improved, lecturing became less of a strain and he gained a few pounds in weight. After one month therapy was discontinued and a high-carbohydrate diet with anticholinergic administration was attempted. He maintained some improvement, but relapsed after two months. In view of the bilious vomiting, intermittent diarrhoea, weight loss and frequent recurrences of dumping, he was subjected to an end-to-side Billroth conversion.

The results of the glucose-tolerance and tolbutamide tests are shown in Fig. 1. Unfortunately he did not return for a test while getting oral hypoglycaemic therapy.

Case 4

W.W., aged 57, was first seen at the Gastro-intestinal Service in May 1962. A Polya gastrectomy without a valve had been done seven years previously for chronic duodenal ulceration. Dumping symptoms became manifest shortly after his operation and consisted of epigastric emptiness, headaches, flushing, slurred speech, ataxia and mild abdominal pain 15 - 30 minutes after a meal. Inability to concentrate at work was an arresting feature. A variety of medical regimes had been tried, with only slight symptomatic relief. A functional component to the symptoms was suspected, but this was disproved by the subsequent course.

At the time of investigation in 1962 his symptoms were so disturbing that he had contemplated suicide. In addition, he had lost a great deal of weight with intermittent steatorrhoea. Barium studies were normal and gastroscopy showed a normal gastric remnant and jejunum. A moderate iron-deficiency anaemia was present and the serum biochemistry was normal. The augmented histamine test showed a histamine-fast achlorhydria. The faecal fat was increased to 10·3 G./day.

Chlorpropamide, 250 mg. daily, with an unrestricted carbohydrate diet was started on 16 May 1962. On subsequent follow-up he no longer had headaches, loss of balance and slurred speech, but was depressed and felt weak. The therapy appeared to exacerbate his steatorrhoea. By 14 July he had maintained this partial recovery, yet he still experienced burning epigastric pain with nausea and felt exhausted. He was discharged on a low-carbohydrate diet, anticholinergics and antacids, and in view of an exacerbation of symptoms two months later coupled with steatorrhoea and loss of weight, an end-to-end Billroth conversion was undertaken. Since this operation he has gained weight, returned to work and been relieved of all dumping symptoms.

RESULTS

Symptomatic Response to Chlorpropamide Therapy

Table I shows the major symptoms, and the length and type of response to chlorpropamide therapy in the four patients. In one patient dumping symptoms disappeared completely, and he was maintained on therapy for four months. A recurrence of symptoms after cessation of

TABLE I. RESULTS OF TREATMENT WITH CHLORPROPAMIDE IN FOUR PATIENTS WITH SEVERE POST-GASTRECTOMY DUMPING

		Dumping symptoms			*Oral hypoglycaemic therapy*		
Case No.	*Age (years)*	*Duration (years)*	*Time after meals (minutes)*	*Type*	*Time in weeks*	*Result*	*Outcome*
1	43	2	20-30	Blurring of vision, faintness, tremor, anxiety, sweating, inability to concentrate	16	Marked improvement. Loss of all symptoms apart from occasional blurring of vision	Maintained on low-carbohydrate diet
				Mild recurrence of symptoms after stopping chlorpropamide	2	Remission of symptoms	
2	35	2	120-180	Lightheaded, tremor, sweating, pallor, inability to concentrate on work	4	Temporary improvement for two weeks. Slight lightheadedness still present. Recurrence of symptoms relieved by addition of anticholinergics	Maintained on low-carbohydrate diet
3	42	3	50-60	Dry mouth, sweating, unsteady gait with tendency to fall to the left. Loss of concentration and memory. Difficulty in lecturing. Biliary vomiting. Diarrhoea	4	Partial improvement. Able to concentrate and lecture. Gait less unsteady. No effect on vomiting	Billroth conversion
4	57	7	15-30	Epigastric emptiness, flushing, slurred speech, ataxia, inability to concentrate. Contemplated suicide. Loss of weight ++. Steatorrhoea	4	Partial improvement. No ataxia or slurred speech. Able to concentrate. Slight gain in weight. Recurrence of symptoms on stopping therapy	Billroth conversion

therapy was again abated by a two-week course of chlorpropamide. A partial remission was obtained in two cases while on trial. These two patients were subsequently submitted to operation for a recurrence of symptoms combined with diarrhoea, loss of weight and bilious vomiting. The one patient with 'late dumping symptoms' remitted temporarily, but slight symptoms recurred while still on chlorpropamide. The addition of an anticholinergic and moderate carbohydrate restriction produced a complete remission.

Biochemical Findings

(*a*) *Glucose-tolerance Tests.* The results of the pretreatment glucose-tolerance tests, glucose-tolerance tests while on chlorpropamide therapy, i.v. tolbutamide tests, and serum potassium and osmolarity are shown in Fig. 1. Before chlorpropamide therapy all the patients showed a marked alimentary hyperglycaemic response and in case 4 the glucose-tolerance tests appeared to be frankly diabetic. The maximal blood-sugar concentration ranged between 230 and 295 mg. per 100 ml. and the time of the peak varied from 30 to 50 minutes after the administration of glucose. Apart from case 4, the blood sugar returned to fasting levels after 120 minutes. The test in the patient

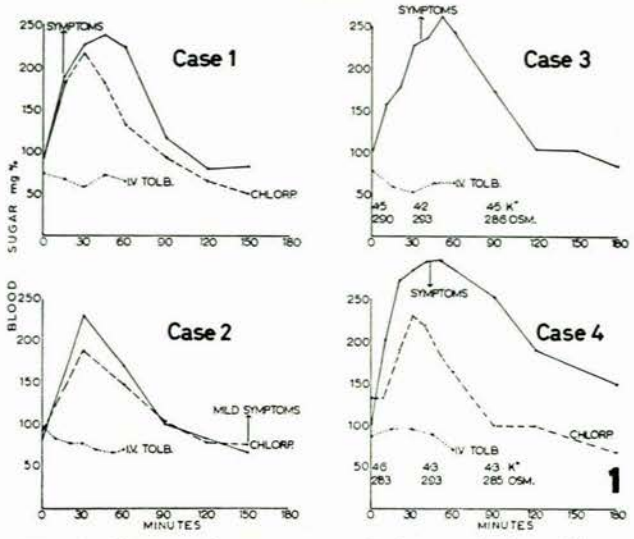

Fig. 1. Glucose-tolerance curves before and after chlorpropamide therapy and during the i.v. tolbutamide tests. In cases 3 and 4, the results of serum-potassium and serum-osmolarity estimations are also shown.

with 'late dumping' did not differ appreciably from the other three, but the graph was continued for only 150 minutes.

A moderate decrease in serum-potassium levels and elevation of the serum osmolarity occurred at the height of reproduced symptoms in the two patients in whom the estimations were carried out.

The results of the glucose-tolerance tests during chlorpropamide therapy showed that the peak blood levels were uniformly reduced; a normal curve was obtained in one (case 2) and in the remaining two the curves were set at a lower level than the pretreatment blood-sugar levels. It is of particular interest that only one patient developed mild dumping symptoms during the chlorpropamide glucose-tolerance test, in contrast to the regularity with which symptoms occurred in the test carried out before commencing therapy.

(*b*) *IV tolbutamide tests.* The results of the i.v. tolbutamide tests in the individual cases are shown in Fig. 1. The maximum hypoglycaemic response was 68% of the fasting level (case 3) and all the curves tended to be flat, with a delay of between 30 and 60 minutes in the appearance of hypoglycaemia. In case 4 the hypoglycaemic response at 60 minutes was in fact preceded by a rise in blood-sugar levels.

(*c*) *Serum insulin-like activity.* The figures for the serum insulin-like activity in the individual cases are given in Table II. In cases 2, 3 and 4 the fasting serum insulin-

TABLE II. SERUM INSULIN-LIKE ACTIVITY, BEFORE AND AFTER CHLORPROPAMIDE THERAPY, ESTIMATED DURING THE GLUCOSE-TOLERANCE TEST

Case No.	*Test*	*Serum insulin-like activity**			
		Fasting	*20 min.*	*30 min.*	*60 min.*
1	Glucose	—	—	—	—
	Glucose and chlorpropamide	427	—	1,007	200
2	Glucose	597	—	—	548
	Glucose and chlorpropamide	608	—	385	60
3	Glucose	479	378	—	200
	Glucose and chlorpropamide	657	—	690	166
4	Glucose	128	818	—	636
	Glucose and chlorpropamide	536	—	1,550	1,042

* Expressed in milliunits per litre.

like activity while the patients were on chlorpropamide therapy was higher than in the pretreatment serum, although the difference was negligible in case 2. Insulin-like activity was also elevated in the 30-minute blood samples during the glucose-tolerance test carried out while on chlorpropamide in cases 1, 3 and 4, and it is perhaps of interest that the patient who did not show this response had 'late dumping' symptoms. The insulin-like activity at 60 minutes was variable. Although grossly increased in case 4, insulin levels were decreased in cases 2 and 3.

DISCUSSION

The basic physiological derangements which contribute to the production of the distressing group of symptoms in the post-gastrectomy dumping syndrome have been the subject of considerable research in recent years. The main stumbling block in arriving at a definitive conclusion has been the lack of consistency between abnormalities found in patients with the dumping syndrome and those patients without dumping. Thus, objective physiological changes, such as elevated blood pressure, electrocardiographic changes, decreased plasma volume, reduction in serum-potassium levels and increase in serum osmolarity, hyperglycaemia and reactive hypoglycaemia, decreased cardiac output, increased renal blood flow, and abnormal intestinal motility, pressure and electrical activity, have been recorded not only in patients with the syndrome, but also

in asymptomatic post-gastrectomy subjects when challenged with a high osmolar meal or solution. Indeed, there has been little correlation between the severity of symptoms and the magnitude of the abnormal physiological aberration. These discrepancies have led Clayman and Kirsner[3] to define the dumping syndrome as 'a homeostatic overaction, comprising a complex of physiological, hormonal and biochemical chain of reactions to altered gastric anatomy which results in the rapid passage of food from the gastric stump into the duodenum and jejunum'. It is apparent, therefore, that one or more factors, such as hypovolaemia, hypokalaemia, hyperglycaemia or hypoglycaemia, distension and mechanical changes, may be operative in the individual subject.

The most consistent finding, however, has been the liability of a high-carbohydrate meal or hypertonic glucose solutions to provoke symptoms or to reproduce the altered physiological state.[4] As early as 1940 Glaessner[5] postulated a state of 'hyperglycaemic shock' based on the frequent occurrence of alimentary hyperglycaemia in these patients. This attractive hypothesis was subsequently discarded after it was found that similar blood-sugar levels occurred in asymptomatic post-gastrectomy subjects after an oral hypertonic glucose solution was administered.

We were sufficiently impressed by the greater rise in blood-sugar levels, following the standard glucose-tolerance test in our patients with severe and persistent dumping symptoms, to speculate whether alimentary hyperglycaemia could not in fact be implicated as the cause of symptoms either directly or indirectly. In this respect it is of particular interest that two of our patients volunteered, as a major feature of their attacks, blurring of vision, a symptom which appears regularly with changes in intraocular glucose concentration in diabetic patients. Apart from the raised blood-glucose levels, individual reactivity to wide blood-sugar alterations over a short period of time may also contribute to the syndrome in those patients with less marked hyperglycaemia.

On these premises it seemed reasonable to attempt to reduce the precipitate rise, peak blood levels and rapid fall of blood-sugar concentration, by ensuring more uniform blood-sugar levels throughout the day by means of a relatively small dose of an oral hypoglycaemic agent. The effectiveness of a low-carbohydrate diet or a diet of low osmolarity in curtailing post-gastrectomy dumping symptoms adds further support to the rationale of employing these agents in such patients. Dietary measures, however, tend to aggravate the distressing loss of weight that most of these patients exhibit. It was hoped that by substituting a hypoglycaemic drug it would be possible not only to suppress symptoms, but also to reinstitute dietary carbohydrates and promote weight gain.

On chlorpropamide therapy one of our patients improved dramatically and treatment could eventually be stopped without further recurrence of symptoms. Two patients showed a partial remission, with gain in weight and diminution of all symptoms, but were subsequently subjected to Billroth conversion owing to a combination of dumping, steatorrhoea, gross initial loss of weight, and vomiting. The remaining patient with late dumping symptoms showed a temporary improvement, but still preferred a reduced carbohydrate intake while on chlorpropamide.

Whereas the present trial was undertaken on an empirical basis, Le Quesne *et al.*[6] have implicated alimentary hyperglycaemia as an indirect contributing factor in the production of the syndrome. By studying the plasma volume with Evans blue dye and varying the circulatory blood volume by cuffs applied to the limbs, they proposed that two factors were important in the production of post-gastrectomy dumping — the size of the fall in plasma volume caused by fluid shift from plasma to jejunum after hyperosmolar solutions, and the resistance of the patient to such fall. In addition, Hobsley and Le Quesne[7] showed that there was a definite correlation between the degree of plasma-volume reduction and the rate of rise of blood-sugar concentration, and postulated that patients with alimentary hyperglycaemia had an altered rate of glucose metabolism in the peripheral tissues. By extrapolation they concluded that peripheral utilization was not fast enough to cope with the rapid glucose absorption. Then the net result of homeostasis would be subsequently diminished glucose absorption with retention in the gut, producing jejunal hyperosmolarity and an osmotic shift of fluid into the gut with resultant hypovolaemia. Following their hypothesis to its logical conclusion, they observed satisfactory symptomatic improvement by the administration of subcutaneous insulin before meals in a number of patients.

Their findings are to some extent supported by the results obtained in the present four cases. A rapid rise to markedly elevated blood-sugar levels occurred in all the patients, with a correspondingly rapid decline. The rise in serum osmolarity at the time of maximal blood-sugar concentration, although slight, suggests fluid shift into the jejunum with subsequent plasma-volume depletion. The reduction in blood-sugar levels following oral chlorpropamide therapy was paralleled by symptomatic improvement, and it is likely that this was affected by the insulin-stimulating properties of the sulphonylurea group of oral hypoglycaemic agents. The higher serum insulin-like activity demonstrated during the glucose-tolerance tests in our patients while receiving chlorpropamide, as compared to the pretreatment levels, would tend to support this pharmacological action. While insulin stimulation is perhaps the predominating effect of these drugs, Radding *et al.*[8] have suggested that additional effects may be alterations in intrahepatic metabolism and suppression of epinephrine-stimulated glycogenolysis.

The results of the i.v. tolbutamide tests were surprising. The vast majority of normal subjects exhibit a marked hypoglycaemic response of the order of 50% of the fasting blood-sugar level within 20 - 30 minutes of the administration of i.v. tolbutamide, according to Unger and Madison,[9] and our own findings in normal subjects agree with theirs. In the four present cases the maximum reduction was 32%, and one patient in fact demonstrated an initial rise in his blood-sugar level. We have since repeated the tests in 12 further patients, with similar results. At present we are unable to account for these findings.

It may be argued that the symptomatic effect of oral hypoglycaemic therapy is non-specific and dependent not only on a closer doctor-patient relationship during the

period of the trial, but also on the stimulating effect of hypoglycaemia on appetite. That psychogenic factors were responsible for the dumping symptoms in these patients is rendered unlikely by the complete cure obtained in two of the patients after Billroth conversion. It has been our experience that dumping symptoms may be precipitated by mental stress and emotional upsets and that the symptoms may persist even after mental equanimity has been restored. Chlorpropamide therapy may be particularly effective in these circumstances, to break what appears to be a vicious circle of reactions.

While the stimulating effect of hypoglycaemia on appetite is undoubted, the improvement in all dumping symptoms cannot be completely accounted for by this mechanism. It would seem likely that the ability of chlorpropamide to prevent large blood-sugar fluctuations in these patients best explains the symptomatic improvement.

It is stressed that this short-term trial of oral hypoglycaemic agents was carried out in patients with severe, persistent and unremitting dumping symptoms. No attempt was made to vary the dosage of chlorpropamide or to include patients with less severe or temporary dumping. Severe and prolonged dumping is rare compared to self-limiting dumping occurring soon after gastrectomy. It is hoped that chlorpropamide therapy will be particularly effective in patients with this early, mild dumping, and that it will obviate the necessity for restricted dietary regimes.

SUMMARY

A short-term trial of oral hypoglycaemic drugs in four patients with severe post-gastrectomy dumping symptoms is presented. A complete remission of symptoms was obtained in one, a partial remission in two, and one patient with the 'late or hypoglycaemic syndrome' exhibited a temporary improvement in symptoms.

Glucose-tolerance tests before and after chlorpropamide therapy in three patients showed that the pretreatment alimentary hyperglycaemia was reduced in all, and in two the rapidity of the rise in glucose concentration was delayed.

Serum insulin-like activity was found to be higher after chlorpropamide therapy when compared with pretreatment levels. Patients with post-gastrectomy dumping symptoms tend to exhibit less marked hypoglycaemia after intravenous tolbutamide than normal controls.

The physiological basis of the symptomatic improvement in postgastrectomy dumping obtained by oral hypoglycaemic drugs is briefly discussed with regard to the pharmacological action of these drugs.

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