Serotonin Antagonists in Experimental and Clinical "Dumping" *

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THE EARLY symptomatic phase of the postgastrectomy dumping syndrome is characterized by a group of subjective changes which can be largely attributed to coincident increases in peripheral blood flow. The over-all pattern of the response tends to be quite consistent between patients, and in severity can be directly correlated to the magnitude of the stimulus and of the increases in peripheral blood flow.[18, 29] The same can be said for the response as induced in Roux-Y (jejunal) fistula dogs.[15, 18, 37]

To account for the very early and widespread changes, several investigators have suggested that a circulating substance may be released on hyperosmolar stimulation of the upper small intestine.[1, 24, 25] We have been able to show that some substance is released into the portal venous plasma of dogs given an intrajejunal hyperosmolar stimulus which, when infused into normal dogs, produces a *dumping* response, with diarrhea, vomiting and increased peripheral blood flow.[17, 19]

Shifting of fluid from the vascular space into the intestinal lumen with a consequent decrease in circulating blood volume has been favored as the cause of symptoms in dumping. Recent experimental findings of Butz and others support our concept that the blood volume decreases, which in time sequence occur later, are not contemporaneous with and hence not involved in the genesis of the *early* symptomatic phase of dumping[6, 26] (Fig. 1).

The humoral agent involved in dumping has not been identified, but on theoretical grounds serotonin (5-hydroxytryptamine) is suspect. It is present in greatest quantity in man in the enterochromaffin cells of the duodenum and jejunum.[16, 27]

Formation, storage and release of serotonin is evidently a continuous process, with a turnover rate such that serotonin stores are replaced each 14 to 24 hours.[10] The amount and rate of serotonin release can be increased by intraluminal pressure, intestinal hypermotility, intraluminal acid, and hypertonic sugar solutions.[2, 3, 5, 25, 28] Most of these factors are present in patients with dumping.

The pharmacologic effects of serotonin are similar in many respects to the pathophysiologic events of both the clinical and

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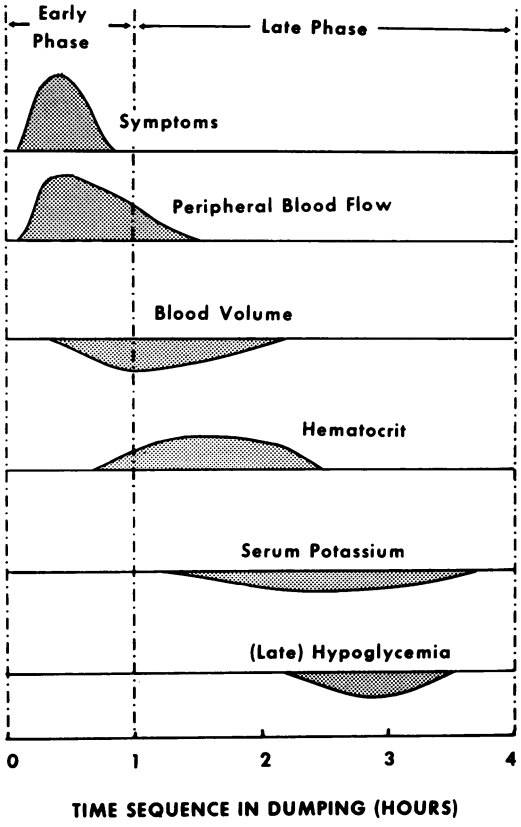

FIG. 1. The early symptomatic phase of dumping, beginning almost immediately after meals, is concomitant with the early increase in peripheral blood flow. The later occurring blood volume, glucose and electrolyte changes are consequences of intestinal hyperosmolarity, and not causes of the earlier symptoms.

the experimental dumping response.[22] Thus in appropriate doses, serotonin exerts the following effects, all of which are identical to those seen following hyperosmolar stimulation of the intestine: decrease in gastric acid secretion; reduction of pancreatic exocrine secretion; intestinal hyperperistalsis and diarrhea, and peripheral vasodilatation with increase in flow rate and pulse pressure.[7-9, 11, 14, 15, 20, 36, 38] This strong inferential evidence, together with the experimental and clinical findings already cited has prompted us to construct a combined clinical and experimental study of certain chemical serotonin antagonists in dumping.

Methods and Results

Experimental Studies

The experimental dumping syndrome was induced in mongrel dogs by instillation of 200 cc. of 50 per cent glucose solution directly into an upper jejunal (Maydl) fistula. Morphine sulfate sedation, 6.0 mg./kg., was employed to keep the dogs quiet but awake, permitting plethysmographic monitoring of peripheral vascular responses by means of a simple mercury strain gauge fastened around the forefoot[34] (Fig. 2). In a previous study, each of nine dogs in a total of 18 tests showed an increase in peripheral blood flow following the stimulus, as measured by an increase in pulse amplitude of 33 to 300 per cent over control levels.[18] The present study utilized nine similarly prepared dogs. Several *dumping* tests were performed on each of the animals, producing consistent increases in peripheral blood flow (Fig. 3).

Twelve studies were then undertaken using three drugs, each of which has a different mode of action on serotonin metabolism. Reserpine releases serotonin from intestinal stores in the enterochromaf-

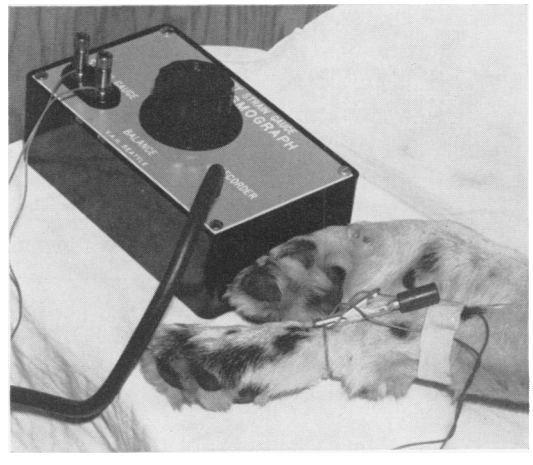

FIG. 2. A simple mercury strain gauge, fastened around the forefoot of a dog, is connected to the plethysmograph matching circuit. With a standard recording machine, this becomes a simple technic for plethysmographic monitoring of peripheral vascular responses in the dog.

fin cells.[3] Alpha-methyl-dopa (Aldomet *) blocks the formation of serotonin from its precursor (5-hydroxytryptophan).[33] Cyproheptadine (Periactin *) is a potent serotonin antagonist equivalent in activity to lysergic acid diethylamide in its ability to inhibit the response of tissues and organs to serotonin.[35] Therapeutic doses of these agents were given to each dog, after which the *dumping* tests were repeated. The drugs, their dosages, and each dog's response to the tests before and during drug therapy are summarized in Table 1. As noted, the increase in peripheral blood flow characteristic of the experimental dumping syndrome was either absent or markedly diminished following treatment with any one of the three drugs.

Profound sedation and diarrhea were apparent at all dosage levels in the dogs given reserpine. Alpha-methyl-dopa produced only mild sedative effects. Cyproheptadine, however, is as effective as reserpine and alpha-methyl-dopa in blocking the vasomotor response to the hypertonic stimulus, without any apparent side-effects in terms of activity and behavior of the animals. Each of the drugs also delayed or prevented diarrhea subsequent to the hyperosmolar stimulus.

* Merck, Sharp and Dohme

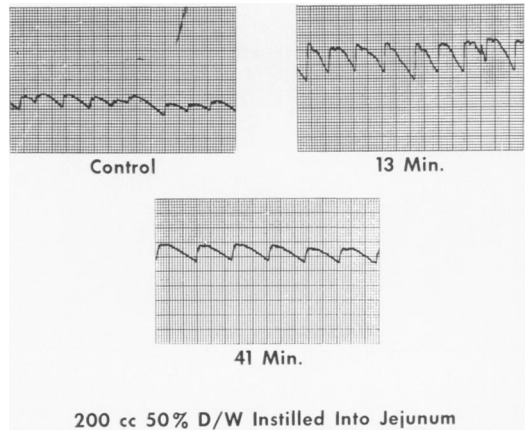

FIG. 3. A plethysmographic tracing of the peripheral vascular response of a dog given a hypertonic intestinal stimulus. Note the increased pulse amplitude, reflecting increased peripheral blood flow, shortly after the stimulus. This is characteristic of the experimental dumping syndrome.

Clinical Studies

Sixteen patients with moderate to severe postgastrectomy dumping for up to nine

TABLE 1. *Experimental Dumping Before and During Treatment*

Dog	Drug	Dose	Increase in Pulse Amplitude with Stimulus	
			Before Treatment %	During Treatment %
J-25	Reserpine	0.5 mg./kg.	150	0
J-27		0.2 mg./kg.	95	0
J-23		0.1 mg./kg.	60	0
J-29		0.1 mg./kg.	90	20
J-35		0.5 mg./kg.	100	0
J-23	A-methyl dopa	85 mg./kg.	60	0
J-20		85 mg./kg.	100	0
J-39		85 mg./kg.	90	0
D-3	Cyproheptadine	2.0 mg.	300	33
D-5		2.0 mg.	100	20
J-20		2.0 mg.	100	0

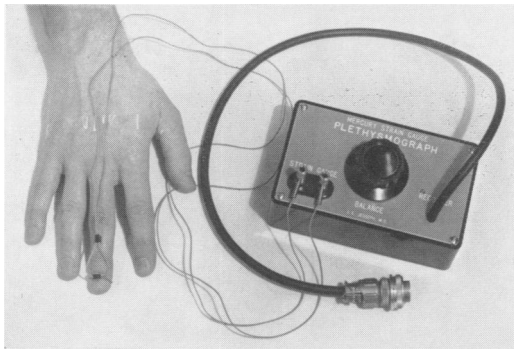

FIG. 4. The mercury strain gauge loop with matching circuit and any standard recorder, provides a simple method of digital plethysmography in patients during a *dumping test*.

years comprise the clinical study to date. Age range is 24 to 65 years; five of the patients are women. The group is evenly divided between those having had a 75 per cent gastric resection and those with hemigastrectomy and vagotomy, except for two patients operated for recurrent ulcer have approximately 90 per cent resections without vagotomy. Ten have gastrojejunal anastomoses, six have gastroduodenal (Billroth I) reconstructions. It is to be noted that this relatively high proportion of gastroduodenal anastomoses may reflect a preponderance of such primary operations in our community rather than a tendency to dumping following such operations.

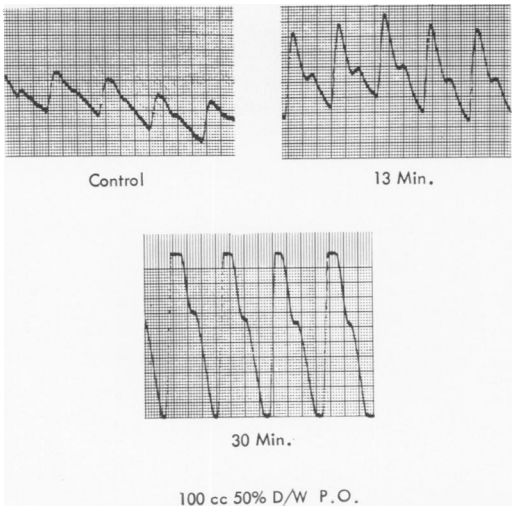

FIG. 5. A digital plethysmographic tracing in a postgastrectomy patient given a hypertonic test meal. The pulse changes represent increased peripheral blood flow, and record early physiologic changes during the symptomatic phase of the dumping sequence.

Each patient was studied in the fasting state. A mercury strain gauge was fastened around the third finger (Fig. 4) for plethysmographic monitoring during the dumping response. After a suitable baseline tracing had been obtained, the patient was given an oral hyperosmolar stimulus of 100 cc. of 50 per cent glucose solution flavored with orange juice. A pulse amplitude increase, as illustrated in Figure 5 was noted in every case indicative of an increase in peripheral blood flow. Concomitant symptoms were recorded. Following this control test, each patient was placed on appropriate doses of alpha-methyl-dopa or cyproheptadine. (Reserpine was not used in patients because of its side effects.) Only two patients were given alpha-methyl-dopa, after which they were changed to cyproheptadine because of orthostatic hypotension. We have found that from 4.0 to 6.0 mg. of cyproheptadine taken about two hours before meals is adequate dosage. Higher doses produce mild sedation but do not increase therapeutic effectiveness.

After a minimum of 24 hours treatment, each patient was retested as before. The drugs, the dosage used, and the symptomatic and vascular responses before and during therapy are summarized in Table 2. It is apparent that the peripheral vascular changes and the symptoms induced by the stimulus were markedly diminished or abolished after institution of drug therapy.

After six months of treatment and observation, all of the patients but one continue to benefit. (The one patient receiving no sustained improvement in symptoms with cyproheptadine was previously relieved by alpha-methyl-dopa, despite mild hypotensive episodes.) All have been gratifyingly free of vasomotor symptoms, most are entirely relieved of explosive episodic diar-

rhea, and most have gained weight. Some report that they are able to eat normally for the first time since operation. Along with these specific signs of improvement, most are notably improved in attitude, ambition and sense of well-being.

Predictably, the patients continue—in variable degree—to have sensations of fullness and nausea, probably related to diminished gastric reservoir. In addition, some continue to have late hypoglycemia with nervousness, sweating and hunger. These effects could not be expected to be modified by anti-serotonin therapy.

TABLE 2. *Dumping in 16 Patients Before and During Treatment*

Patient	Drug	Daily Dose	Increase in Pulse Amplitude with Stimulus	
			Before Treatment %	During Treatment %
D. D.	Cyproheptadine	18 mg.	150	0
R. E.	Cyproheptadine	12 mg.	100	0
H. F.	Cyproheptadine	12 mg.	43	0
S. H.	Cyproheptadine	24 mg.	274	125
	Alpha-methyl-dopa	1.5 Gm.	274	75
D. I.	Cyproheptadine	12 mg.	110	0
D. L.	Cyproheptadine	12 mg.	150	0
W. M.	Cyproheptadine	18 mg.	400	0
	Alpha-methyl-dopa	1.5 Gm.	400	0
R. M.	Cyproheptadine	12 mg.	300	0
D. P.	Cyproheptadine	12 mg.	144	0
P. R.	Cyproheptadine	12 mg.	100	33
E. R.	Cyproheptadine	12 mg.	40	0
T. R.	Cyproheptadine	12 mg.	133	0
E. T.	Cyproheptadine	18 mg.	500	0
J. W.	Cyrpoheptadine	18 mg.	500	23
D. W.	Cyproheptadine	12 mg.	60	22
E. Z.	Cyproheptadine	12 mg.	140	0

Two brief case reports will illustrate the nature and degree of dumping in this group of patients, as well as response to treatment.

Case Reports

Case 1. A 48-year-old white laborer, 6′6″ in height, had weighed only 170 pounds since hemigastrectomy, vagotomy and Billroth I reconstruction one year before study. Within a few minutes after each meal he experienced severe flushing, sweating and weakness regularly, followed by several episodes of watery diarrhea. The whole complex prostrated him for periods up to two hours. Treatment with cyproheptadine resulted in marked relief of all symptoms, and there was almost complete reversal of plethysmographic changes. The patient promptly gained 10 pounds, and has been able to return to work.

Case 2. A 48-year-old nurse anesthetist had two gastric resections for duodenal ulcer and stomal recurrence, with only about 20 per cent of stomach remaining. At a height of 5′5″, she could maintain a maximum body weight of only 92 pounds, and had been severely malnourished and anemic. She always had severe vasomotor and gastro-intestinal symptoms after meals. After three weeks of cyproheptadine therapy, the patient had gained 10 pounds, and was free of vasomotor changes and weakness. There was also marked improvement in plethysmographic response. Despite this improvement, the patient continues to have fullness and limited capacity for food.

Discussion

The peripheral blood flow change in dumping has been well described.[7, 15] It occurs simultaneously with the symptomatic period and tends to parallel the severity of the symptoms.[18] Measurement of this change by plethysmography is the best objective test currently available to assess the presence and severity of the dumping syndrome. Thus, a change in the peripheral blood flow response to a hypertonic stimulus in any given patient is probably a reliable index of the extent and range of physiologic derangement. Similarly, a decrease or elimination of peripheral vasodilation while under treatment is a reliable objective measure of therapeutic effectiveness.

The three drugs, reserpine, alpha-methyldopa and cyproheptadine do not depress capactiy for vasomotor reaction in the dog. During testing, each continues to vasoconstrict in response to noise or painful stimuli, and retains the reactive hyperemia response.

Each of the three drugs used in the experimental studies has a different mode of pharmacologic action with respect to serotonin activity in the animal. The three agents individually also have other pharmacologic activities, including anti-histaminic properties and reduction of sympathetic amine production,[33, 35] but these probably are incidental to their effects in dumping. The fact that these anti-serotonin drugs decrease or abolish the peripheral vascular response to the intestinal hypertonic stimulus lends support to the concept of a serotonin mechanism in dumping.

The entire group of patients improved by plethysmographic test, and had diminished or absent symptoms after a test meal. Most of the patients continue to show striking symptomatic improvement and are able to eat a more nearly normal diet. The majority of patients have gained weight. Several of the patients had post-prandial diarrhea which has ceased during treatment with cyproheptadine. These responses to treatment with serotonin antagonists adds further credence to the implication of serotonin in the genesis of dumping.

In view of the accumulated evidence to date, the pathophysiology of the dumping syndrome may be represented as follows. Rapid *dumping* of carbohydrate or fatty (hyperosmolar) food into the upper small bowel often occurs in patients after gastric surgery[21, 23] (Fig. 6). This may be related to a small residual gastric reservoir, but not to stoma size.[32] It is possible that gastroduodenostomy affords some protection against rapid emptying due to the sphincteric action of anti-peristalsis in the duodenum, and may be preferable for this reason.[21]

A large bolus of hypertonic food ma-

terial is physiologic only to the duodenum, and only then in quite small volumes.[31] The magnitude of symptoms and physiologic changes in dumping is directly related to the size of the hypertonic stimulus.[30] With outpouring of intestinal secretion to dilute the contents to isotonicity, increased intraluminal pressure, distension and hypermotility rapidly occur. These factors (in addition to hyperosmolarity) are known to cause release of stored serotonin into the intestinal lumen and into portal venous blood.[2, 5, 25] The free serotonin (or related substance) circulating systemically, may act to increase peripheral blood flow with consequent symptoms of flushing and sweating, while the gut is stimulated directly, with hypermotility, cramps and diarrhea.[4] With continued dilution of intestinal contents, a gradual reduction in blood volume occurs. Instead of physiologic protective vasoconstriction in the face of a diminishing circulatory volume, the peripheral vascular bed under the influence of a potent vasodilator substance fails to maintain homeostasis by increasing peripheral resistance. In such a situation, if the patient is kept upright, he experiences hypotension, weakness and general worsening of symptoms.[7]

Other measurable physiologic changes follow. With relative hemoconcentration the hematocrit rises. Alimentary hyperglycemia occurs with absorption of large amounts of glucose (if available from the meal) evoking a vigorous insulin response. Glucose utilization produces a decrease in serum potassium and consequent electrocardiographic changes. Finally, with the insulin surge, blood glucose may fall to hypoglycemic levels producing the late symptoms of sweating, nervousness, hunger and even convulsions two to six hours after eating.

Shortly after a dumping episode with release of available serotonin, the patient may find he can eat with only minimal symptoms or none at all. However, with re-accumulation of serotonin stores during an overnight fast, the patient frequently finds his most severe symptoms occur after breakfast. One might even correlate the nutritional disturbances, and weight loss of the postgastrectomy syndrome with the hypermotility and decreased pancreatic secretion induced by serotonin.

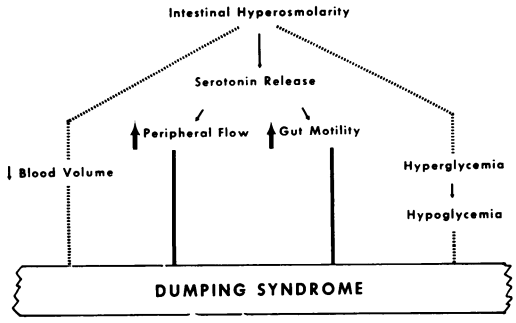

FIG. 6. A diagrammatic representation of the possible pathophysiology in the dumping syndrome. The symptomatic phase of dumping reflects primarily the vasomotor and gastro-intestinal effects of a serotonin intermediary mechanism. The blood volume and glucose changes, directly related to intestinal hypertonic carbohydrates, probably play a secondary and later role, respectively.

Further evidence of the role of serotonin in dumping awaits its demonstration as a circulating agent in increased concentration in the systemic blood of animals or patients with the experimental or clinical dumping syndrome. Such studies are currently in progress.

The clinical implications of the present study are intriguing. If dumping is a biochemically mediated phenomenon, it seems ideal to treat it by specific biochemical means. Serotonin antagonists do not relieve *all* postgastrectomy problems, and particularly not those of epigastric distress, nausea, or the hypoglycemic symptoms, all of which can be explained without invoking a humoral agent. But the results to date are most encouraging in terms of amelioration of many of the distressing aspects of dumping. Some of the serotonin antagonists are now available and are safe without significant side effects. Extended clini-

cal trials with these agents will be of interest.

Our work with *medical* treatment of dumping began at a time when one of us (H. N. H.) became especially interested in some of the newer operative technics for dumping.[12, 13] We can say definitively, however, that in the light of our preliminary results with the medical treatment of dumping and despite our interest in the operative methods, at this time we could not justify operation in any of the 16 consecutive cases of dumping reported in this study.

Summary

The early symptomatic portion of the postgastrectomy dumping syndrome is characterized as a complex of vasomotor and gastro-intestinal disturbances consequent to the delivery of hyperosmolar solutions into the small bowel.

The increase in peripheral blood flow as measured by plethysmography, characteristic of the experimental dumping syndrome in dogs, can be prevented by the prior administration of reserpine, alpha-methyldopa, or cyproheptadine, three agents of differing pharmacologic properties having, in common, anti-serotonin activity.

Plethysmographic evaluation of 16 moderate to severe dumping patients using an oral hyperosmolar *dumping test*, revealed striking decreases in the peripheral vascular response in all patients during administration of a serotonin antagonist, cyproheptadine.

In all but one patient, the marked improvement in vasomotor symptoms and diarrhea noted during the *dumping test* has been sustained for periods up to six months, with weight gain in the majority of patients. No benefit was apparent in the epigastric discomfort associated with a large meal, nor in the *late* hypoglycemic symptoms.

These findings substantiate the concept that serotonin may be the humoral intermediary agent in the production of the early, symptomatic phase of dumping.

The use of serotonin antagonists in postgastrectomy dumping patients is recommended before consideration of operative means of treatment.

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