The Pentagastrin Test in the Diagnosis of the Carcinoid Syndrome

Blockade of Gastrointestinal Symptoms by Ketanserin

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The levels of 5-hydroxytryptamine (serotonin, 5-HT) and substance P (SP) were assayed (using high performance liquid chromatography-electron capture and radioimmunoassay methods) in the peripheral blood of 17 patients with known mid-gut carcinoids, 16 of whom had hepatic metastases. All patients had supranormal basal levels of 5-HT and SP. The clinical and hormonal changes induced by two provocation tests, intravenous pentagastrin (PG) and calcium infusion, were compared. Pentagastrin caused flushing in all the patients, induced gastrointestinal symptoms in all but one of the patients with hepatic involvement, and universally elevated circulating 5-HT levels. Pretreatment with a 5-HT_2-receptor blocking agent, ketanserin, abolished the gastrointestinal effects but had virtually no influence on either 5-HT levels or flushing induced by intravenous pentagastrin. In contrast, calcium infusion induced carcinoid symptoms in only two of six patients, and this was consistently associated with stimulation of circulating serotonin levels. The authors conclude that 1) 5-HT may be responsible for the gastrointestinal symptoms in carcinoid patients, but it does not seem to play any role in flushing; 2) ketanserin may be a useful therapeutic agent in alleviating gastrointestinal symptoms in carcinoid patients; 3) differential responses to PG suggests that SP is released from a site different from that of 5-HT; 4) it is possible that SP may contribute to the mediation of flushing, but it cannot be the sole agent causing this symptom; and 5) the pentagastrin test with measurements of 5-HT levels in peripheral blood seems to be superior to calcium infusion as a provocative test in documenting the diagnosis of carcinoid disease.

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THE APUD CONCEPT[1] implies that biologically active peptides and amines may be synthesized and stored within the same endocrine cells. This is exemplified by the enterochromaffin cells (EC), which store both serotonin (5-HT)[2] and substance P (SP),[3] possibly within the same secretory granules.[4]

Patients with the carcinoid syndrome have elevated levels of 5-HT in peripheral blood,[5,6] and the tumors contain large amounts of the amine.[7] 5-HT has been ascribed a major role in the development of diarrhea,[8-10] but not in flushing, since intravenous administration of 5-HT does not induce a facial flush.[11,12] Recently, SP has been identified in mid-gut carcinoid tumors.[4,13] Since SP is a potent vasodilator[14] and infusion of this peptide induces facial flushing, SP must be considered as a potential mediator of this reaction.

We have reported previously that calcium infusion was useful as a provocative test in the diagnosis of the carcinoid syndrome,[15] and that there were considerable similarities in the hormonal responses of patients with carcinoids and those with medullary carcinomas of the thyroid.[16] Since pentagastrin has been utilized as a provocative test in patients with medullary thyroid carcinoma,[17] the present study was initiated to evaluate the pentagastrin (PG) test in the carcinoid syndrome. The purpose of the study was to 1) establish whether PG induced vasomotor and gastrointestinal symptoms in patients with carcinoid tumors; 2) correlate the development of such symptoms with changes in peripheral levels of 5-HT and SP; 3) compare the effects of this challenge with those elicited by provocation with calcium infusion; and 4) evaluate the effects of treatment with ketanserin, a peripheral 5-HT_2 receptor blocking agent (which has no effect on SP),[18,19] on the elicited subjective symptoms and induced changes in blood levels of 5-HT and SP.

Material and Methods

Patients

Seventeen carcinoid patients (ten men and seven women), aged 47–84 years, agreed to participate in this

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TABLE 1. *Patient Population*

Patient No.	Sex	Age	Flushing		Diarrhea	Medic for Diarrhea	Asthma	Treatment		Urinary 5-HIAA* (μmol/day)	5-HT† (ng/ml)
			4/day	Telangiectases				Tumor Resection	Liver Rx		
1	M	70	+	+	++	+		+	—	382	743
2	F	72	+		+	+	+	+	—	174	343
3	F	57	+		++	+		+	Embolization	201	355
4	M	75	+		+			+	—	229	150
5	M	69			++	+		−	IA 5-FU + Streptozotocin	170	763
				+							
6	M	70			++	+	+	−	—	321	477
7	M	66	+	+	++	+		+	Artery Ligation	135	95
8	M	73			+			+	—	—	100
9	M	65	+		++	+		+	Resection + IA 5-FU	604	144
10	M	65	+		++	+		+	IA 5-FU + Streptozotocin	482	240
11	M	68	+		+			+	Artery Ligation	—	201
12	F	84			++	+		+	Embolization	196	205
13	M	62	+		+	+		+	IA 5-FU	132	134
14	F	61	+	+	+	+		+	IV Streptozotocin	—	138
15	F	57	+		+			+	IV Streptozotocin	—	266
16	F	47	+		++	+		+	IV Streptozotocin	146	2,386
17	M	52						+ with Omentectomy	—	70	183

* Normal <80 μmol/day.

† Normal <100 ng/ml.

protocol (which was approved by the Ethical Committees of the University of Göteborg, the University of Uppsala, and the Downstate Medical Center). Sixteen of the patients had mid-gut carcinoids with massive hepatic metastases, and all of those tested had elevated rates of urinary excretion of 5-hydroxyindole acetic acid (5-HIAA) (Table 1). Sixteen had undergone intestinal surgery, and eight had surgical procedures directed against their hepatic metastases (one liver resection, four hepatic artery ligation or embolization [one with intraarterial 5-FU], and three hepatic arterial perfusion with strepozotocin and/or 5-FU) prior to this study. All patients with hepatic metastases had gastrointestinal symptoms with as many as 15 bouts of diarrhea daily; 12 required medication for profuse diarrhea at the time of the study. In addition, 12 patients had at least four episodes of flushing daily, two had severe bronchoconstrictive attacks, and four had facial telangiectases. One patient had an omentectomy and ileal resection for a carcinoid involving regional lymph nodes 1 year earlier, at which time there was no hepatic involvement. At presentation, this patient had had persistent diarrhea and flushing, symptoms that disappeared after the ileal resection. After surgery, 5-HIAA excretion rates also returned to normal levels. At the time of the present test protocol, extensive radiologic investigations (including ultrasound and CAT scan) were negative, repeated determinations of 5-HIAA excretion were normal, and we cannot document that the patient has hepatic metastases (see Addendum). In addition, five healthy noncarcinoid patients participated as controls.

Determination of 5-HT

Blood samples were drawn twice before (basal levels) and 1, 3, 5, 10, and 15 minutes after pentagastrin (PG) injection (0.6 μg/kg, i.v. over 30 seconds), and every 30 minutes during the 3-hour intravenous calcium gluconate infusion (4 mg/Ca^{++}kg/hr). Whole blood samples of 1.0 ml were added to heparinized glass tubes containing 4 ml of distilled water and stored on ice. After hemolysis was complete, precipitation with $ZnSO_4$ and NaOH was performed,[20] the samples were centrifuged at 3000 rpm for 20 minutes, and the sediments were discarded. In parallel samples, known amounts of 5-HT creatinine sulfate (25 – 100 pmol) were added to control tubes to correct for recovery. Analyses were performed using a method of high performance liquid chromatography with electrochemical detection (LCEC) originally developed for measurement of 5-HT in small tissue samples.[21] The supernatants were added to the columns in 10-μl aliquots without further processing. Recovery of authentic 5-HT added averaged 72 ± 5%. Standard curves were made by injecting standard solutions ranging from 2.5 – 10 pmol in 10 μl prepared by dissolving 5-HT creatinine sulphate in 0.1 m perchloric acid. In one patient, 5-HT levels were measured using a radioimmunoassay developed in our laboratory.[22]

Determination of SP

Blood samples were collected according to the same time schedules as for 5-HT. Samples were centrifuged for 10 minutes at 3000 rpm and 4 C and the sediments were

discarded. SP was extracted sequentially from aliquots of plasma using ammonium sulfate and ethanol; the samples were lyophilized and reconstituted in one-fourth the original volume. SP concentrations were measured using a sensitive (< 1.0 pg/ml plasma), and specific radioimmunoassay system developed in our laboratory.[23] This assay does not cross-react with 5-HT or any known human peptide hormone.

Study Protocol

Twelve patients (11 with hepatic metastases) had PG-provocative tests without ketanserin pretreatment. Six of them also had calcium infusion on a separate day. On still another day, 11 of these patients and four additional ones were pretreated with ketanserin (10 mg intravenously) and 10 minutes later, the PG challenge was repeated. A final patient with carcinoid syndrome was subjected to all three provocations, except that she was pretreated with 20 mg of ketanserin orally every 12 hours for three doses prior to the repeat PG test.

Five noncarcinoid patients (four women and one man) whose ages ranged from 25 to 52, served as controls for the PG test (obviously without ketanserin).

Results

Pentagastrin Test

Injection of pentagastrin induced a brief (up to 1 minute) subjective and objective facial flush in all patients within the first 2–3 minutes after injection. A slight decrease in blood pressure (<20 mmHg) also was recorded. The patients with hepatic disease also developed gastrointestinal symptoms (urgency, borborygmi, and/or colicky cramps). These symptoms accompanied the flush but generally lasted somewhat longer, up to 5 minutes.

All the patients had elevated blood levels of 5-HT. Overall, the mean basal 5-HT level for the group was 252 ± 56 ng/ml (mean ± SEM). The average response to PG infusion is demonstrated in Figure 1. Using Student's t-test for paired data, the mean values at 1 and 3 minutes were significantly higher than basal ($p < 0.05$). Peak values occurred within 5 minutes in 10 of 13 patients and by 15 minutes in the remainder. The mean peak value, 422 ± 71 ng/ml, was also significantly different from the average basal level ($p < 0.001$). Increases of 40% above basal or peak minus basal differences of > 50 ng/ml occurred in all the patients with hepatic metastases; the only patient who failed to meet either criterion was Patient 17, in whom hepatic metastases were seemingly absent. In Patient 16, the 5-HT level rose from 2386 ng/ml basally to a peak of 3108 ng/ml at 10 minutes; although she clearly had a positive response, she

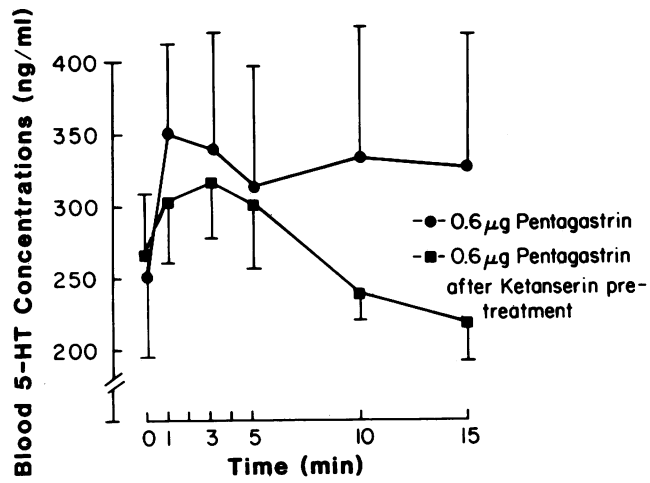

FIG. 1. 5-HT levels in peripheral blood following intravenous pentagastrin provocation in carcinoid patients without any treatment (N = 13) (O) and after pretreatment with ketanserin (N = 15) (X). Data represent means ± SEM.

was excluded from the above averages because her levels were so extremely high. In general, the gastrointestinal complaints occurred at or about the time that 5-HT levels peaked.

In contrast, basal 5-HT levels in the noncarcinoid patients averaged 46 ± 10 ng/ml ($p < 0.01$ vs carcinoid basal values). None of them became symptomatic as a result of the infusion and 5-HT levels were not stimulated (values averaged 39 ± 16, 39 ± 16, and 37 ± 14 ng/ml at 1,3, and 5 minutes, respectively).

SP levels were determined during the PG test in four patients. All these patients had elevated basal levels of SP varying between 42 and 79 pg/ml (mean 57 ± 8; normal < 10 pg/ml). SP levels did not increase in *any* of the patients challenged.

Pentagastrin Test After Ketanserin

After ketanserin pretreatment, injection of PG-induced similar symptoms of flushing in all but one of the patients, but the flushes were less severe. However, in contrast to the studies performed without ketanserin, seven of the patients with hepatic metastases developed very mild gastrointestinal symptoms in response to pentagastrin, and eight were relieved totally. There was no correlation between prevention of gastrointestinal complaints and changes in 5-HT levels.

The 15 patients in this group had mean basal blood levels of 5-HT (268 ± 40 ng/ml) and responded with average augmented 5-HT levels, which were not significantly different from the increases noted in the absence of ketanserin (Fig. 1). The mean peak level, 356 ± 38 ng/ml, was significantly greater than basal ($p < 0.05$) but not significantly different from the comparable data

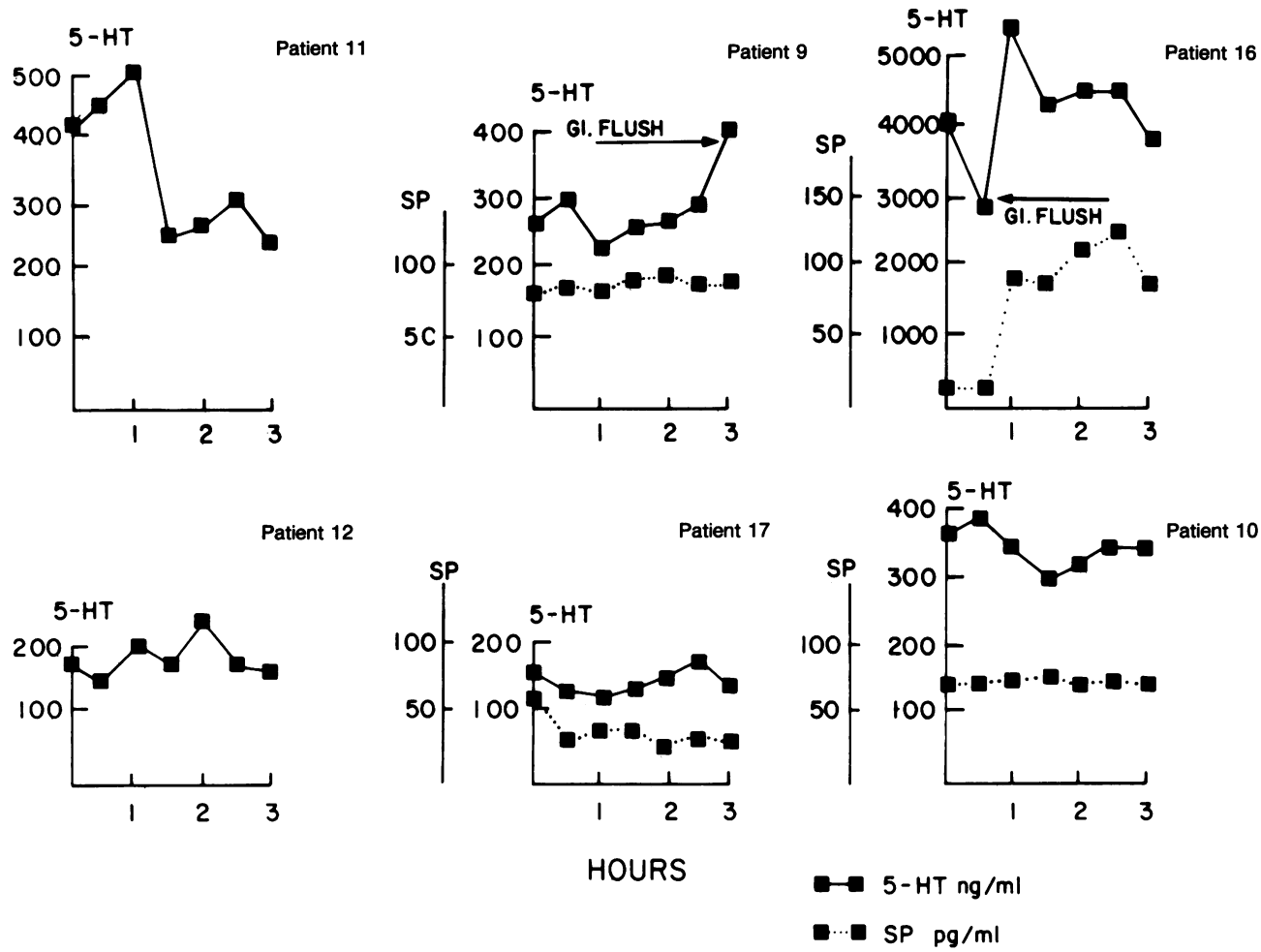

FIG. 2. Five-HT (O) and SP (X) levels in peripheral blood and specific symptomatology following provocation by calcium infusion in the six carcinoid patients.

without ketanserin. Peaks occurred within 5 minutes in 13 of 15 patients. Only one patient, not tested without ketanserin pretreatment, did not have a significant rise in 5-HT levels as defined above; we have no explanation for this anomaly, and it must be considered a false-negative test.

The mean basal levels of SP in the four patients tested were similar to those recorded without ketanserin except in Patient 17 whose level of 10 pg/ml contrasted to the previous value of 42 pg/ml. After PG stimulation, SP levels in Patient 9 increased from 66 to 112 pg/ml synchronously with the flush symptoms, but Patient 17 demonstrated a late (15 minutes) 30 pg/ml increase in SP unrelated to the early flush symptoms.

Calcium Infusion

Only two of six patients tested developed symptoms in response to calcium. Three hours after the onset of infusion, Patient 9 noted both flushing and diarrhea at which time infusion was interrupted. At the time of flushing and diarrhea, a sharp rise in the 5-HT level was recorded while SP concentrations remained at a high but constant level. Patient 16 developed flushing and cramps within 1 hour and these symptom persisted for the duration of the infusion. The data are displayed individually in Figure 2.

Mean basal SP levels were consistently elevated as before, but there was a significant increment in circulating SP during calcium infusion only in Patient 16, which correlated with the onset of flushing. In contrast, there was no change in plasma SP levels in Patient 9, who developed a bout of flushing.

Discussion

In patients with mid-gut (argentaffin, argyrophilic) carcinoids, 5-HT is by far the most common amine secreted and thus, patients with mid-gut carcinoids have elevated basal levels of 5-HT in peripheral blood. In contrast, patients with foregut tumors have high circulating levels of 5-hydroxytryptophan[24-26] yet normal blood levels of 5-HT. Although 5-HTP is not decarboxy-

lated by platelets,[11,27] decarboxylation may occur in the kidney; in this circumstance, the newly formed 5-HT escapes oxidation and is secreted into the urine.[26] When quantitating blood levels of 5-HT, it is of considerable importance to use a method that specifically detects only 5-HT and not 5-HTP or any of its metabolites. Recent radioimmunoassay and LCEC-techniques provide the necessary specificity.[21,22]

All the patients in the present study had mid-gut carcinoids. Eleven of the 12 patients tested had elevated 5-HIAA levels at the time of the study and one patient had elevated levels prior to resectional surgery 1 year earlier. It was of interest to note that the patients with most pronounced gastrointestinal symptoms also had the highest rates of urinary excretion of 5-HIAA, since a correlation between the severity of diarrhea and urinary 5-HIAA has been postulated previously.[28]

Pentagastrin has been used as a provocative test for medullary carcinoma of the thyroid,[17] somatostatinoma,[29] and three patients with carcinoid tumors (one gastric and two intestinal[30,31]). In our experience, using the pentagastrin test, all patients developed facial flushing, a symptom that did not occur in our controls and does not occur in healthy subjects given pentagastrin. Furthermore, all the patients with hepatic metastases developed gastrointestinal symptoms in response to the PG provocative test. On the other hand, in contrast to our previous observations,[15] only two patients developed symptoms during calcium infusion. Thus, this study suggests that the clinical reliability of the PG test seems to be superior to that of calcium infusion,[15] a point for which we have no explanation. It is important to point out, however, that one patient had a false-negative PG stimulation test. The positive clinical response and elevated basal levels of 5-HT and SP in Patient 17 suggests that covert and currently undiagnosed tumor exists in this patient; he will be subjected to future PG-testing in combination with extensive diagnostic procedures.

All 16 patients with known hepatic metastases demonstrated increased 5-HT levels synchronous with their induced gastrointestinal symptoms. After peripheral specific blockade of 5-HT_2 receptors by ketanserin, release of 5-HT by PG was not prevented yet gastrointestinal symptoms virtually were aborted totally. This suggests that the intestinal symptoms were mediated by the amine.[32,33] Further evidence for 5-HT as the diarrhoegenic messenger was obtained from one patient, who responded to the calcium infusion test, and in whom gastrointestinal symptoms occurred synchronously with a dramatic increase in 5-HT but no change in plasma SP levels. Since three patients were taking diphenoxylate for severe diarrhea, and they seemed to benefit from ketanserin during the PG test, they were allowed to continue this drug orally (10 mg twice daily) after completion of the studies. These patients were totally relieved of diarrhea within one week, but only one patient experienced any decrease in flushing. Patient 12 electively stopped the medication after 1 month while patient 9 has continued this therapy for 6 months and has remained completely free of gastrointestinal symptoms.

All four patients in whom the SP levels were followed had markedly elevated basal peptide levels but experienced no significant incremental change in response to pentagastrin. Furthermore, during calcium infusion, T.B. developed flushing unassociated with any change in SP levels. Since this peptide is released independently of 5-HT, our data suggests that 5-HT and SP are not stored in the same granules. This is supported by our recent report of a mid-gut carcinoid with breast metastases, which demonstrated, using immunocytochemistry, that SP and 5-HT occurred in separate populations of tumor cells.[34]

The exact etiology of carcinoid flushing remains unknown. The observation that the symptom is abolished by infusion of somatostatin[30,35] suggests that it is humorally medicated. Bradykinin[11] and prostaglandins[36] have been proposed as modulators but the evidence is far from conclusive. Although the biologic actions of SP are consistent with the manifestations of the carcinoid syndrome,[37] the current study demonstrates that this peptide is not the sole mediator of this symptom.

In conclusion, the results of our study suggest that the pentagastrin test may be the most valuable provocative test in the diagnosis of the carcinoid syndrome associated with liver metastases. Enhanced peripheral blood levels of 5-HT accompanied characteristic symptoms, which were evoked in all patients tested. In patients with known hepatic disease, gastrointestinal symptoms were induced in addition to facial flushing. Peripheral blockade of 5-HT_2 receptors did not affect the release of 5-HT, but it virtually aborted the PG-induced gastrointestinal symptoms without consistently preventing the associated flushing. Pentagastrin did not alter SP levels, even in patients who developed flushing, suggesting that this peptide can be released from tumor independently from 5-HT and that it is unlikely to be the sole mediator of flushing.

Addendum

Several months after submission of the manuscript, the pentagastrin test converted to positive (while 5-HIAA, CAT scan, and angiography remained normal). At operation, multiple intraabdominal and hepatic metastases were noted.

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