Case report

Pathophysiological study of diarrhoea in a patient with medullary thyroid carcinoma. Evidence against a secretory mechanism and for the role of shortened colonic transit time

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SUMMARY   Intubation techniques and scintigraphic studies were used to determine the origin and mechanism of diarrhoea in a patient with medullary thyroid carcinoma, high plasma immuno-reactive calcitonin and normal circulating serotonin, substance P and prostaglandins E_2 and $F_{2\alpha}$. Normal function of the small intestine was found for the following: (a) absorption tests; (b) water and electrolyte absorption in the proximal jejunum; (c) 24 hour flow rate and composition of fluid entering the colon and (d) gastric emptying rate and small intestinal progression of a normal meal. By contrast, colonic function was markedly impaired in three ways: (a) water absorption was decreased by half; (b) as the main excreted solutes were organic acids, a large electrolyte gap was recorded in faecal water, and (c) colonic transit time of the meal marker was very short, and was in agreement with the rapid transit of ingested radioopaque markers. These data strongly suggest that decreased absorption in the colon secondary to a motor disturbance is the main mechanism of diarrhoea in this case of medullary thyroid carcinoma, while calcitonin induced small intestinal fluid secretion suggested earlier is either non-existent, or only of minor importance.

Diarrhoea is seen in 28–39% of patients with medullary thyroid carcinoma (MTC).[1,2] The link between tumoral secretion and diarrhoea is obvious as the latter is more frequent in patients with advanced disease,[3,4] immediately disappears after complete surgical resection of the lesion[3,5] and relapses in cases of tumour recurrence.[3] Because an acute intravenous infusion of calcitonin induces jejunal and ileal secretion of water and electrolytes in normal man,[6] the diarrhoea accompanying MTC is usually considered to result from a secretory process induced by raised circulating calcitonin.[7] Calcitonin production by MTC is a constant feature, however,[8] whether or not diarrhoea is present, and its plasma concentration does not seem to correlate with intestinal dysfunction.[4]

We report here a pathophysiological study of the increased faecal fluid losses in a case of MTC with diarrhoea and hypercalcitoninaemia. The results do not support the presence of a secretory mechanism, but strongly suggest that diarrhoea was the result of dysfunction of the colon caused by a marked shortening of the transit time of the intraluminal contents.

Case history

A 41 year old man was admitted to hospital for chronic diarrhoea which had lasted for eight years. He passed six to 15 watery stools per day; motions were urgent and mainly postcibal, and the faeces

often contained undigested foods absorbed during the preceding meal. Four years previously, a thyroid nodule, several enlarged cervical lymph nodes and a calcified lung miliary had been found. Subtotal thyroidectomy was done, and pathological examination revealed a typical medullary carcinoma with amyloid stroma. Personal and familial past histories were unremarkable. On admission, the patient had lost 20 kg of weight. There were frequent abdominal borborygmi and slight hepatomegaly. Several cervical lymph nodes were enlarged. In other respects, physical examination was normal, and blood pressure was 120–80 mm Hg.

Haemogram, plasma glucose, serum urea, electrolytes, calcium, inorganic phosphorus, and 24 hour urinary calcium and magnesium outputs were normal. Carmin red oro-anal transit time was 150 min. Daily stool number and weight (mean of three days) were 12 and 1003 g respectively, and decreased to four and 567 g during the daily oral administration of 43 mg codeine and 36 mg codethyline. In the absence of these drugs, stool weight dropped to 420 g during the second day of a 48 hour fast. Faecal fat (mean of three days) was 5·8 g/d. D-xylose and Schilling's tests were normal, and so was the cholyl-^{14}C-glycyl breath test. Sigmoidoscopy, barium enema, and follow through showed no morphological abnormalities, but the swallowed barium reached the caecum and rectum within 30 and 60 minutes respectively. Liver and skeletal scintiscans revealed several secondary deposits. Patient immunoreactive plasma calcitonin was markedly raised (266 ng/ml, normal <0·25 ng/ml). There was a superposition of the dilution curve for the patient's immunoreactive plasma calcitonin and the standard curve for calcitonin radioimmunoassay with synthetic human calcitonin. No salmon like calcitonin was detected by a specific radioimmunoassay. The concentration of patient's calcitonin, assessed in the same plasma sample by a biological assay,[9] was abnormally high (115 ng/ml, the normal level being undetectable in this assay) although lower than the result given by the radioimmunoassay. Plasma concentrations of immunoreactive prostaglandins E_2 (11 pg/ml) and F_2 (9 pg/ml), substance P, gastrin, vasoactive intestinal peptide, somatostatin, and parathormone were all

normal. So were plasma serotonin and cortisol, and 24 hour urinary outputs of 5-hydroxy-indolacetic acid, of catecholamines and of their metabolites vanillylmandelic and homovanillic acids. The total plasma thyroxin concentration was low, but triiodothyronine and thyroid stimulating hormone concentrations were normal.

Methods

SUBJECTS
The patient and healthy volunteers were studied after obtaining their written informed consent and the approval of the local ethic committee.

INTESTINAL PERFUSION STUDIES
Jejunal perfusion
Transintestinal water and electrolyte transport in the absence of non-electrolyte solutes was measured in the proximal jejunum by the triple lumen tube perfusion technique.[10] The test solution (130 mM NaCl, 20 mM KCl, polyethylene glycol 4000 PEG 1 g/l) was perfused at a rate of 8 ml/min. The mixing and test segments were 20 cm and 25 cm long, respectively. Stimulation of sodium and water transport by glucose was studied distal to an occluding balloon (test segment 25 cm). The test solutions (130 mM NaCl, 5 mM KCl, PEG 10g/l, 30 mM mannitol or glucose) were perfused at a rate of 10 ml/min. Results of these two studies were compared with those previously obtained in our laboratory in 18 and 10 healthy volunteers, respectively.[10 11]

Slow marker perfusion studies
The overall small and large intestinal transport of water and electrolytes was determined by simultaneous measurement for 24 h, by the slow marker perfusion technique, of the flow rate and composition of the fluid entering the jejunum and leaving the terminal ileum, and by collecting all stools during the three days preceding the perfusion study. This study was done with a previously described several lumen tube.[12] Tube 1 was used to perfuse, in the duodenum 15 cm proximal to the angle of Treitz, ^{57}Co-vitamin B_{12} (4 μCi/l in NaCl 150 mM) at a constant rate of 0·5 ml/min. Tube 2, ending 15 cm below near the angle of Treitz, allowed sampling of intestinal contents at the same rate of 0·5 ml/min. Tubes 3 and 4, ending 30 cm apart, were used to perfuse ^{14}C-PEG (60 μCi/l in NaCl 150 mM) 40 cm above the ileocaecal function at a constant rate of 0·25 ml/min and to aspirate intestinal contents as completely as possible in the terminal ileum. All four tubes were tracted by tube 5 ended with a mercury bag that could be inflated with air to hasten tube progression. When the bag had reached the caecum, it was deflated and the subject was asked to maintain a semirecumbant position to

Table 1   *Jejunal perfusion study with triple lumen tube*

	H_2O (ml)*	Na (μmol)*	Cl (μmol)*
Patient	+0·08	+7·8	+3·6
Controls (mean (2 SD) n=18)	−0·77 (0·84)	−89 (98)	−131 (140)

*Dates are expressed per min and per 25 cm; + =net secretion;
− =net absorption.

avoid further progresson of the tube. Tubes 1 and 2 were bound to the tracting tube in such a way that they could be separated from it when their distal openings were correctly positioned. The number of control healthy volunteers was limited to three, as the ileal results were within the range of values found by us[13] and others[14] using cold PEG as non-absorbable ileal marker. During the whole study, the patient and the controls received the same low fibre diet containing 2225 kcal, 74 g proteins, 81 g lipids, 300 g carbohydrates, and 1500 ml water/24 h.

Analytical procedures

Sodium and potassium were measured by flame photometry, and chloride and bicarbonate, by a colorimetric method on a Technicon auto-analyser. Stool water volume was calculated from the difference between fresh and dry weights. Stool electrolytes, ammonium and total organic acids were measured according to Goiffon *et al.*[15][16] Osmolality of extracellular stool water obtained by centrifugation was determined immediately after their recovery

Table 2   *Jejunal perfusion studies distal to an occluding balloon**

	H_2O (ml)	Na (μmol)	Cl (μmol)
Mannitol solution			
Patient	0·0	−10	−52
Controls†	−0·27 (1·04)	−68 (162)	−69 (146)
Glucose solution			
Patient	−2·6	−328	−369
Controls†	−3·37 (1·56)	−407 (236)	−423 (266)
Δ net movement‡			
Patient ·	−2·6	−318	−317
Controls†	−3·6 (2·4)	−477 (376)	−490 (380)

*Data are expressed per min and per 25 cm.
†Mean (2 SD) n=10.
‡Difference in water and electrolyte transport when glucose replaces mannitol in the perfused solution. Sign − =increased absorption.

with a Fiske osmometer. Results were compared with those obtained in five healthy volunteers whose stools were appropriately diluted before centrifugation. [57]Co and ^{14}C radioactivities were measured with a gamma counter (CGR-SAIP France) and liquid scintillation counter (Intertechnique France), respectively.

Calculations

Water and electrolyte movements and the enhancement of electrolyte and water transport by glucose during segmental perfusion studies, and flow rates at the ligament of Treitz and in the distal ileum, were calculated according to the usual formulae.[10][11]

GUT TRANSIT TIME

Radioopaque markers

The mean transit time of radioopaque markers was determined by the single stool method[17] before codeine and codethyline administration and during this treatment and compared with values obtained without any treatment in 15 healthy volunteers.

Scintigraphic study

Gastric emptying and intestinal progression of a normal solid-liquid meal were investigated in the patient according to a previously published technique,[18] using [99m]technetium sulphur colloid (^{99m}Tc) as marker. Results obtained were compared with those previously found in 16 healthy controls.[18]

Results

JEJUNAL AND ILEAL SEGMENTAL PERFUSION

In the jejunum, water, sodium and chloride movements during the perfusion of a pure electrolyte solution with the triple lumen tube were within normal confidence limits (Table 1). During the jejunal perfusion distal to an occluding balloon,

Table 3   *Twenty four hour flow rates of water and electrolytes at the angle of Treitz, in distal ileum, and in stools*

	H_2O (ml)	Na (mmol)	K (mmol)	Cl (mmol)	HCO_3 (mmol)
Treitz angle					
Patient	4265	455	40	436	63
Controls (range, n=3)	3765–4959	391–553	39–50	405–437	47–59
Distal ileum					
Patient	2280	306	16	235	92
Controls (range, n=3)*	2127–2761	261–365	15–39	194–338	40–86
Stools					
Patient	1171	59	40	88	18
Controls (range, n=3)	80–222	1·2–11·5	7·5–23·5	1·1–5·5	0·2–1·5

*In four other controls in whom cold PEG was used instead of ^{14}C-PEG as marker of water movements, flow rates in distal ileum per 24 h were 2080 (140) ml, 280 (15) mmol, 14 (1) mmol, 235 (13) mmol, and 56 (12) mmol (mean SE) for water, sodium, potassium, chloride, and bicarbonate respectively.[13]

Table 4 *Twenty four hour movements of water and electrolytes in the small intestine (jejunum+ileum) and the colon**

	H_2O (ml)	Na (mmol)	K (mmol)	Cl (mmol)	HCO_3 (mmol)
Small intestine					
Patient	−1985	−149	−24	−201	+29
Controls (range, n=3)	−1638 to −2308	−130 to −214	−11 to −24	−199 to −211	−7 to −13
Colon					
Patient	−1119	−247	+24	−147	−74
Controls (range, n=3)	−2047 to −2539	−260 to −354	−7 to −15	−193 to −332	−40 to −84

*Sign − =absorption, sign + =secretion.

water, sodium and chloride movements were also normal with both mannitol and glucose containing solutions, whereas glucose absorption was slightly depressed. Stimulation of jejunal sodium and water absorption by glucose, estimated as the difference observed between sodium and water movements with the glucose and mannitol containing solutions, was normal (Table 2).

SLOW MARKER PERFUSION
The 24 hour fluid and electrolyte flow rates at the ligament of Treitz and in the distal ileum were within the normal range, except for the bicarbonate rates which were slightly increased at both levels (Table 3). The overall jejunoileal transport of water and ions, calculated as the difference between the flow rates in the distal ileum and at the angle of Treitz, was normal except for bicarbonate (Table 3). Faecal water and electrolyte outputs were raised (Table 3). Comparison of ileal and faecal outputs showed that colonic water absorption was markedly low, whereas sodium absorption was only slightly below the lower control limit (Table 4). There was a mild colonic secretion of potassium, instead of absorption in the controls, and chloride absorption was moderately reduced (Table 4).

Faecal water osmolality, measured in four different stools, ranged between 362 and 380 mosmol/kg.

The solute content of the same faecal water samples is given in Table 5. Although 24 hour faecal organic acid output could not be calculated exactly from these data, it is clear that it was markedly raised, compared with normal controls. Moreover, it is noteworthy that faecal water osmolality was much higher than the product [Na+K]×2, where [Na] and [K] were the concentrations of sodium and potassium in the same faecal water samples, respectively.

GUT TRANSIT TIME
Mean total transit time of radioopaque markers was 3·6 h (normal values 44 (15) h) without treatment, and 6·5 h and 8·3 h under 43 mg codeine and 36 mg codethyline. Scintigraphic study of the progression of the solid-liquid meal showed a normal gastric emptying rate (emptying half time: 84 min, normal 68 (31) min, mean (SD), range 30–135, n=16). Progression of the meal through the small intestine was almost normal. The terminal ileum was reached 10 minutes after the end of meal ingestion (normal: 20 (16) min, range 5–65, n=15), and the percentage of ingested radioactivity found in the colon was slightly raised until the 90th minute, when it was 19% (normal: 9·7 (4·8)%, range 2–17, n=16). After this time, the abnormalities of colonic transit described below made further quantification of small bowel emptying impossible, because of colonic superposition. Indeed,

Table 5 *Solute concentrations and osmolality of extracellular stool water**

	Osmolality (mosmol/kg)	Na (mM)	K (mM)	Ca (mM)	Mg (mM)	NH_4 (mM)
Patient†	358 (337–385)	67 (58–76)	29 (25– 36)	27 (25–29)	10 (9–12)	18 (12–22)
Controls‡	384 (297–471)	28 (9–51)	67 (54–126)	18 (12–32)	20 (11–33)	27 (10–60)

	Cl (mM)	HCO_3 (mM)	PO_4 (mM)	Total organic acids (mM)
Patient†	65 (48–88)	15 (11–20)	18 (15–20)	114 (98–126)
Controls‡	14 (7–24)	4 (2– 9)	37 (14–84)	166 (130–222)

*Results are expressed as means; range is in brackets; †Four individual stools of the patient were assayed; ‡Controls were the one day stool of five healthy subjects.

the radioactivity entering the caecal area was almost immediately expelled toward the colonic right angle, and after 90 minutes, the marker was propulsed by successive waves up to the sigmoid area. At 115 min, the patient had a motion containing meal marker as intracolonic activity immediately decreased thereafter (Figure). In the 16 normal controls, the meal marker progressively accumulated in the caecal area and was never propulsed beyond the colonic right angle during the 150 minutes of the study.

Discussion

Previous pathophysiological studies of two cases of MTC with diarrhoea led to the conclusion that the increased faecal output of water and electrolytes was caused by the impairment of small intestine function.[19 20] In our patient, however, the 24 hour flow rates measured for water and electrolytes at the end of the ileum do not support this conclusion. Apart from a slight excess for bicarbonate, they were within the normal range determined in healthy controls. As water and electrolyte flow rates at Treitz's angle were also normal (except for the slightly raised bicarbonate), the overall handling of water and ions in the small bowel of our patient was normal.

The results of the segmental perfusion studies in the proximal jejunum fit this conclusion as the transport of water and electrolytes from a pure electrolyte solution was normal, as was the stimulatory effect of glucose on water and sodium absorption. These findings are in agreement with those of Isaac et al.[19]

As the entry of fluid in the colon of our patient was normal, increased faecal water losses were caused by insufficient net absorption in this organ. In the case studied by Cox et al,[20] ileal fluid flow rate was moderately high, but still well under the maximal capacity of the colon to absorb water.[21 22] The case report of Norman and Otnes[23] illustrates both the possibility of mild bowel dysfunction in MTC with diarrhoea, and its lack of significance in terms of overall intestinal fluid handling. Thus, after an unjustified colectomy, the daily ileostomy output was only 700 g, but dropped to 350 g after resection of the thyroid tumour.

The sum of the sodium and potassium concentrations in stool water of our patient was rather low, whereas faecal water osmolality was greater than that of plasma. Consequently, there was a large gap between faecal water osmolality calculated from its electrolyte content,[7 24] and the osmolality actually measured. Organic acids accounted for most of this 'solute gap'. The pathophysiology of diarrhoea in MTC therefore appears very different from that of secretory diarrhoeas, such as pancreatic cholera.[24]
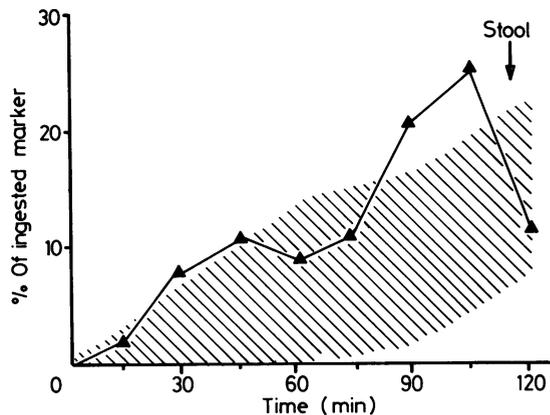
Figure *Percentage of ingested marker counted in the colonic area. The first postprandial stool (+115 min) eliminated 50% of the intracolic activity. Hatched area= range of normal values obtained in 16 healthy subjects (18); none of them had a motion during the study.*

The organic acid concentration of faecal water in our patient was similar to that found in our normal controls and in those studied by Rubinstein et al.[25] On the other hand, faecal water output was markedly higher than in normal subjects; thus, although the output of 24 hour faecal organic acid could not be exactly calculated from our data, it was obviously very high. This in turn could be because of either an increased production of volatile fatty acids by colonic bacteria or decreased absorption in the colon, secondary to the very short transit time of colonic contents.[26] Excess intracolonic fermentation of carbohydrates was unlikely, because in our patient, as in most of the others studied,[5 27] functional tests evaluating the absorption of nutrients in the small bowel were normal. Our scintigraphic investigation of the gut transit of a solid-liquid meal provides an explanation for these findings, as it showed that gastric emptying and small bowel transit were within nearly normal limits. By contrast, the very short transit time of colonic contents found in other patients studied with barium follow through[5] was confirmed in the present case by measuring gut transit time with radioopaque markers, and by scintigraphic assessment of the progression of a normal meal.

Diarrhoea in MTC has been repeatedly related to increased circulating concentrations of calcitonin[7 19 20] because this hormone is known to stimulate secretion by the small intestine mucosa, when acutely administered to normal man.[6] Our present findings and those of Isaac et al[19] do not support this hypothesis. It is not known why, in these two patients, the marked increase in circulating immunoreactive calcitonin (266 ng/ml and 278 ng/ml [19] v 1·8 to 2·4 ng/ml in

Gray *et al* acute experiments [6]) failed to induce secretion of water and ions in the jejunum. Calcitonin has been shown to be present in several different molecular forms in MTC.[28] In our case the result of the biological assay ruled out the possibility that immunoreactive calcitonin was mainly present in biologically inactive form. One explanation might be tachyphylaxia of intestinal mucosa during chronic hypercalcitoninaemia, as a similar mechanism was shown to account for the absence of hypocalcaemia in MTC.[29]

It is also unlikely that hypercalcitoninaemia was responsible for the striking reduction of colonic transit time in the present case, as in all other patients with MTC and diarrhoea.[5 27] Diarrhoea has not been reported as a side effect in patients treated chronically with calcitonin for osteoporosis or Paget's disease, although acute intravenous infusion of about a one day therapeutic dose can induce diarrhoea in the postcibal period.[30] Circulating prostaglandins E_2 and $F_{2\alpha}$, serotonin and substance P can be increased in patients with MTC[31-34] and could be involved in the pathogenesis of diarrhoea. Some of the patients with MTC and diarrhoea, including our present case, however, have normal circulating concentrations of these agents.

Thus, at least in the present case, the diarrhoea associated with MTC does not seem to be caused by a secretory process induced by hypercalcitoninaemia. A dysfunction of the colon, probably secondary to the marked shortening of transit time in this organ, appears to be the main mechanism causing diarrhoea. The humoral agent responsible for this motility disorder remains to be discovered.

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