Circulatory collapse in a patient with gastrinoma after metoclopramide administration

A patient who was given metoclopramide for vomiting and diarrhoea developed circulatory collapse with his blood pressure dropping to 50/20 mm Hg. A gastrinoma was diagnosed histologically. The extent of the tumour was defined by octreotide scanning and magnetic resonance imaging. Metoclopramide was again given for colicky abdominal pain and the patient developed circulatory collapse a second time. A laparotomy involving extensive resection of the tumour was performed. The MEN1 mutation was not detected in blood or tumour tissue. Follow-up octreotide scanning did not show any residual tumour. Possible causes for the circulatory collapse are discussed. Our case is probably the first patient with gastrinoma to develop circulatory collapse after being given metoclopramide.

Case report

Our patient is a 17-year-old boy who had a 3-year history of ulcer symptoms, diarrhoea, and abdominal colic. A year ago he developed gastro-intestinal bleeding, which required blood transfusion. Oesophagogastroduodenoscopy showed a peptic ulcer so he was treated with omeprazole and became asymptomatic. He presented with vomiting and diarrhoea and was admitted with a diagnosis of traveller's diarrhoea.

He was given metoclopramide intravenously to manage his symptoms. His clinical condition deteriorated rapidly with his blood pressure dropping to 50/20 mm Hg. He was admitted to the intensive care unit with pneumonia, rhabdomyolysis, renal tubular necrosis, and disseminated intravascular coagulation.

Enteroscopy showed mild haemorrhagic gastritis and a small mucosal nodule in the antrum. Histological examination of biopsy specimens showed carcinoid tumour. An octreotide scan (6.3 mCi In-111 octreotide IVI, planar imaging from skull vertex to knees at 4, 24 and 48 hours, and single photon emission computed tomography of abdomen at 4 and 24 hours) showed three discrete foci with increased somatostatin receptor expression in the upper abdomen, compatible with tumour lesions at the gastric antrum, near the free edge of segment III of the liver and at the hepatic hilum (Fig a). Magnetic resonance imaging (MRI) demonstrated the segment III lesion in the liver. Contrast computed tomographic scanning of the abdomen showed a 2.7-cm nodule posterosuperior to the gastric antrum and two 2-cm nodules in the left lateral lobe of the liver. Endoscopic ultrasonography showed a 6 mm x 9.5 mm hypoechoic submucosal lesion in the antrum and a 2-cm metastasis at the left lobe of the liver.

His daily urinary excretion of 5-hydroxyindole acetic acid (5-HIAA) was normal but his whole blood serotonin level was raised (428 ng/ml; reference range, 50-200 ng/ml). His serum chromogranin A was also increased (395 ng/mL; reference level, <160 ng/mL) [Table]. His serum histamine and vasoactive-intestinal peptide levels were normal. He was given omeprazole, and all his symptoms resolved. Both his body weight and haemoglobin increased.

His serum gastrin was measured preoperatively and omeprazole was withheld for hormonal assessments. The night before the hormonal assessment, he had abdominal pain and vomiting although an H₂-antagonist had been prescribed, so he was given metoclopramide. His condition deteriorated rapidly and his blood pressure dropped to 90/50 mm Hg. He was resuscitated with a plasma expander and inotropes. His fasting serum gastrin was 3651 pmol/L (reference level, <55 pmol/L) and gastric pH was 1.4. Subcutaneous octreotide and oral omeprazole were given and continued until surgery. Postoperatively both medications were decreased gradually.

During surgery, a 4-cm tumour mass at the hepato-gastric ligament and a 1-cm tumour mass near the free edge of segment III of the liver were seen (Fig b). Enlarged lymph nodes were noted at the first and second part of the duodenum, the tail of the pancreas and the origin of the hepatic artery. All tumours and enlarged lymph nodes were excised. Histological examination of the stomach and lymph node specimens showed features of
Gastrinoma with circulatory collapse

A patient with vomiting and diarrhea developed vasovagal collapse after taking metoclopramide (479). The blood pressure fell to 50/20 mm Hg. Histological examination revealed a gastrinoma. MRI and an octreotide scan were performed to determine the extent of the malignancy. Three lesion sites were identified: the stomach, liver, and lymph nodes. The patient was treated with chemotherapy but his condition deteriorated. After repeated octreotide scans, no new foci of tracer uptake were seen. The patient's serum levels of serotonin and chromogranin A were within the normal range. A genetic analysis of the MEN1 gene was carried out but no mutations were detected.

Discussion

Neuroendocrine tumours (NET) account for about 1.25% of all malignancies. Their incidence has increased due to increased awareness, the availability of sensitive immunohistochemical markers, and better imaging techniques. The classical carcinoid presentation with diarrhea, facial flushing, broncho-pulmonary constriction and right heart failure is uncommon.

After a histological diagnosis of gastrinoma had been made, MRI and an octreotide scan were performed to chart the extent of the malignancy. Three lesion sites were identified: the stomach, liver, and lymph nodes. The patient was treated with chemotherapy but his condition deteriorated. After repeated octreotide scans, no new foci of tracer uptake were seen. The patient's serum levels of serotonin and chromogranin A were within the normal range. A genetic analysis of the MEN1 gene was carried out but no mutations were detected.

**TABLE. Biochemical results**

<table>
<thead>
<tr>
<th>Test</th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>Reference range/level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole blood serotonin (ng/mL)</td>
<td>428</td>
<td>331</td>
<td>50-200</td>
</tr>
<tr>
<td>Serum chromogranin A (ng/mL)</td>
<td>395</td>
<td>77</td>
<td>&lt;160</td>
</tr>
<tr>
<td>Fasting serum gastrin (pmol/L)</td>
<td>3651</td>
<td>53</td>
<td>&lt;55</td>
</tr>
<tr>
<td>Daily urinary 5-HIAA* excretion (mmol/24h)</td>
<td>30</td>
<td>-</td>
<td>&lt;32</td>
</tr>
</tbody>
</table>

* 5-HIAA denotes 5-hydroxyindole acetic acid

There are several ways of classifying carcinoid tumours. They can be classified according to the embryonic origin of the tumour cells, the foregut (stomach, pancreas, and duodenum), midgut (beyond the Treitz ligament of the duodenum to the proximal part of the transverse colon), and the hindgut (the...
distal part of the colon and rectum. The World Health Organization has classified NET in accordance with their size, proliferation, localisation, degree of cell differentiation and hormonal production. Neuroendocrine tumours are classified into well-differentiated NET, well-differentiated NET with low-grade malignancy, and poorly differentiated NET with high-grade malignancy. The term carcinoid is not outdated and is synonymous with ‘well-differentiated NET’.3

In our patient, the challenge was to search for the cause of his circulatory collapse, which was accompanied by several complications. There are a few possibilities. The first is an idiosyncratic reaction with hypotension. The second is an excessive response to serotonin autoinhibition. In the periphery, serotonin (5-HT) is present in both the enterochromaffin cells of the mucosa, which facilitates secretion, and neurons of the myenteric plexus, which facilitates peristalsis. In the central nervous system, serotonin is a neurotransmitter for anger, aggression, mood, appetite, and metabolism. Metoclopramide has both agonistic and antagonistic effects. Apart from being a dopamine D2 receptor antagonist, metoclopramide is a mixed 5-HT3 receptor antagonist and 5-HT4 receptor agonist. Its anti-emetic properties stem from its dopamine D2 receptor antagonistic action in the chemoreceptor trigger zone. The catastrophic autonomic dysregulation seen in our patient may have been due to excessive serotonin autoinhibition. In one reported case, metoclopramide was administered before the patient developed cardiac arrest. The role of metoclopramide in this death was uncertain because several agents were given. In another report, six patients had transient hypotension for 60 to 90 seconds with no permanent damage. Our patient was administered metoclopramide for its peripheral action. It was after the second episode of hypotension that we suspected metoclopramide might have caused his circulatory collapse.

The third possibility is the gastrinoma itself since shock is a rare presentation for gastrinoma. Our patient developed pain and colic when omeprazole was withheld for hormonal assessment. The onset of circulatory collapse after the metoclopramide injection may have been coincidental. A literature search failed to find any reports of metoclopramide-related circulatory collapse in patients with gastrinomas.

Gastrinomas can occur as either the sporadic form or the multiple endocrine neoplasia type 1 (MEN1)–associated form. The two forms have different management and prognosis. The familial syndrome is reportedly present in 25% of gastrinomas, and MEN1 gene mutations are found in 31% of sporadic gastrinomas. A mutation analysis was therefore performed to identify any germline mutations in the MEN1 gene in this patient. Despite the young age of onset and the aggressive behaviour of the tumour, no germline mutation was identified in the MEN1 gene, making familial MEN1 unlikely although our mutation analysis method did not rule out exonic mutations in promoter or other intronic regions.

Neuroendocrine tumours secrete several hormones, particularly those sited in the midgut. Hormone secretion, such as plasma neurokinin A, has high prognostic value. An increase in neurokinin A deserves further imaging for detecting tumour recurrence. In our patient, who has foregut NET, whole blood serotonin and serum chromogranin A levels returned to lower levels after surgery. Chromogranin A is a hydrophilic glycoprotein and is one of the hormones that can be detected in NET. Blood chromogranin A has high sensitivity (99%) for NET but is not specific and can be detected in other tumours such as small cell lung tumours and prostate tumours. False elevation of chromogranin A has also been seen in chronic renal failure, atrophic gastritis and in patients using proton pump inhibitors. Unfortunately, these markers are not easily available in most clinical laboratories, most of which only provide 5-HIAA as a routine screening test; 5-HIAA is usually normal in patients with foregut and hindgut carcinoids. It is important to use the right biochemical tests, maintain high levels of clinical suspicion and to persevere.

**Conclusion**

Our patient is probably the first patient with gastrinoma who developed circulatory collapse after metoclopramide injection. Repeated postoperative octreotide scans found no residual lesions. Biomarker assessments and radiological investigations are appropriate investigations for follow-up.

**References**


