

Short Report

Symptom scores, serotonin and 5-hydroxyindole acetic acid levels in cancer patients with and without bowel obstruction

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Some 40% of patients with advanced ovarian cancer, and 10% of patients with colon cancer, experience bowel obstruction as a complication of disease.¹ Animal studies have shown that both increased luminal pressure,² and ischaemic injury,³ evoke measurable increases in serotonin (5HT) from small bowel mucosa. These reports suggest that both the pressure and ischaemic consequences of malignant bowel obstruction (particularly small bowel) could cause release of 5HT in humans. Released 5HT binds to terminal vagal afferents triggering nausea, before being metabolised in the liver to 5-hydroxyindole acetic acid (5-HIAA), an established mechanism in chemotherapy-induced emesis.⁴

Two previous studies have examined 5HT in bowel obstruction. In 40 patients with non-malignant bowel obstruction, elevated plasma 5HT was found in acute mechanical obstruction, but not in paralytic ileus or chronic obstruction.⁵ The second study (published abstract) found elevated urinary 5HT in 13 patients with obstruction compared with 15 patients without, all of whom had ovarian cancer.⁶

We wanted to examine symptom scores and serotonin in patients with malignant bowel obstruction. Our hypotheses were that patients with malignant bowel obstruction would have more severe symptom scores compared with non-obstructed groups, and that symptom scores would correlate with levels of 5HT and 5-HIAA.

Patients and methods

We recruited adult female patients who gave informed written consent to take part in the study. We studied

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patients with malignant bowel obstruction from ovarian cancer ('obstructed group') defined as meeting the following clinical criteria: colicky abdominal pain plus no flatus for 12 hours, plus at least two of the following features (a) nausea, +/- vomiting, (b) abdominal distension on examination, (c) abdominal radiograph with signs of intestinal distension, air/fluid levels or absence of gas in colon. This group was contrasted with three non-obstructed comparison groups, all of whom had cancer; patients with ovarian cancer receiving platinum-based chemotherapy ('chemo group'), patients with ovarian cancer not receiving chemotherapy and not obstructed ('advanced ovarian group'), and female patients with non-abdominal advanced cancer who were not receiving chemotherapy ('advanced non-ovarian group'). Patients were recruited from St James's University Hospital and St Gemma's Hospice, Leeds. The study received approval from Leeds Teaching Hospitals ethics committee.

We collected data from patients on age, cancer diagnosis (if in 'advanced non-ovarian group') and performance status, using the Eastern Cooperative Oncology Group (ECOG) scale, rated 0 = 'fully active' to 4 = 'completely disabled'. We asked all patients to rate the severity of any nausea on a numerical rating scale anchored 0 = 'no nausea' to 10 = 'worst nausea possible', and we asked the number of times they had vomited in the last 4 hours.

We took a blood sample from all patients and analysed this for whole blood 5HT, plasma 5-HIAA, platelet count and creatinine. We chose blood, rather than urine, in order to detect early changes in biochemical markers. Interviews and blood sampling were undertaken during a single consultation and occurred between 4 and 8 hours after chemotherapy infusion (for the 'chemo group'), between 24 and 48 hours of diagnosed bowel obstruction ('obstructed group'), and electively for the remaining two groups. We compared 5HT and 5-HIAA between groups and standardised these measurements using 5HT to

platelet ratio and 5-HIAA to creatinine ratio because 5HT is sequestered in platelets and 5-HIAA levels are very sensitive to renal impairment.

We based our estimate of power on the data from Hutchinson *et al.*,⁶ who found a 50% difference in urinary 5HT between their groups. We estimated that 15 patients would be needed in each group to provide 80% power with 5% (two-sided) significance level of detecting a 50% difference in 5HT/platelet ratio between the obstructed group and the non-chemotherapy control groups. We used the Kruskal–Wallis and Mann–Whitney tests to examine differences in symptom and ECOG scores between the groups. ANOVA and Student's *t*-test were used to examine differences in biochemical markers between groups.

Results

Over a two-year period, we recruited 15 patients each to the three comparison groups, but only 10 patients were recruited to the 'obstructed group'. Mean age of all 55 patients was 61 years (SD: 10.8), and median ECOG score was 1 (interquartile range: 0–2). Patients within the 'advanced non-ovarian group' had cancers of breast or lung.

Patients with malignant bowel obstruction had significantly more nausea than patients in the 'chemo' ($P = 0.01$) and 'advanced ovarian' ($P = 0.02$) groups, but had similar symptom severity to patients in the 'advanced non-ovarian' group ($P = 0.22$) (Table 1). Performance status was worst for the 'obstructed' and 'advanced non-ovarian' groups, and correlated with symptom scores: nausea ($P = 0.002$) and vomiting ($P = 0.008$). Analysis of variance showed no significant difference between biochemical markers across the four groups (Table 1). There was no statistical relationship between symptom scores and biochemical markers within the whole sample.

Discussion

We have found no indication that symptoms of nausea and vomiting in female patients with advanced ovarian or non-ovarian cancer are related to levels of systemic 5HT and 5-HIAA. The values for 5HT that we obtained were comparable with the normal reference range used by Leeds Teaching Hospitals biochemistry laboratory of 0.5–7.0 nmol/L whole blood 5HT per 10^9 platelets. However, apart from the 'chemo' group, all other groups had moderately elevated 5-HIAA compared to reference value of <70 nmol/L.⁷ Interestingly, Lee *et al.*,⁸ found that mean plasma 5-HIAA was almost five times greater in 40 patients with cancer compared to 165 healthy controls; 8.87 $\mu\text{g/L}$ (49 nmol/L) versus 1.94 $\mu\text{g/L}$ (10 nmol/L), respectively. Both sets of data suggest that 5-HIAA is generally higher in cancer patients compared to normal controls.

We recognise that our study has a number of limitations. The first is that it may have been underpowered, despite our efforts over a two-year period. This is partly explained by the difficulty in recruiting frail and often terminally ill patients, between 24 and 48 hours after onset of bowel obstruction.

The second limitation is that the active comparison group (the 'chemo' group) showed low levels of symptoms and biochemical markers, contrary to what we expected. We were confident that the sampling frame was consistent with previously documented increases in 5-HIAA between 4 and 8 hours following cisplatin.⁹ We recognise that antiemetic regimens prior to chemotherapy might have worked well and attenuated symptoms, though this would not affect levels of 5-HIAA.

Previous research suggests that the rapid release of 5HT from the bowel mucosa occurs between 4 and 20 hours after insult, and this is strongly associated with symptoms of nausea and vomiting. Beyond this period, there is a fall to baseline levels of 5HT and 5-HIAA following emetogenic chemotherapy,⁹ and in the context of chronic mechanical obstruction or ileus.⁵

Table 1 Comparison of symptom scores, ECOG and biochemical markers between study groups

	'Obstructed' (<i>n</i> = 10)	'Chemo' (<i>n</i> = 15)	'Advanced ovarian' (<i>n</i> = 15)	'Advanced non-ovarian' (<i>n</i> = 15)	P value (ANOVA)
Symptom scores					
Nausea score, 0 = 10 scale mean (SD)	2.5 (2.1)	0.07 (0.26)	0.27 (0.8)	1.7 (2.6)	<0.001
No. of vomits in previous 4 hours mean (SD)	0.8 (0.92)	0.0 (0.0)	0.1 (0.26)	0.6 (1.2)	0.019
ECOG scores median (IQR)	3.0 (2.0–3.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	2.0 (2.0–3.0)	0.001*
Biochemical markers mean (95%CI)					
Creatinine $\mu\text{mol/L}$	73 (53–93)	76 (55–98)	85 (69–101)	115 (75–154)	0.09
Platelets 10^9	248 (151–346)	254 (204–305)	267 (186–348)	376 (283–470)	0.04
5HT nmol/L	580 (260–899)	413 (275–551)	506 (333–678)	647 (389–904)	0.37
5HT nmol/L per platelets 10^9	2.54 (0.38–4.7)	1.61 (1.21–2.00)	2.12 (1.1–3.15)	1.79 (1.21–2.37)	0.56
5HIAA nmol/L	78 (44–111)	63 (49–78)	85 (56–114)	111 (66–157)	0.16
5HIAA nmol/L per creatine $\mu\text{mol/L}$	1.1 (0.73–1.47)	0.75 (0.57–0.93)	1.07 (0.67–1.47)	1.03 (0.77–1.3)	0.31

Our study failed to find a relationship between symptoms and significantly elevated 5HT or 5-HIAA levels associated with these mechanisms. We did, however, find that the significantly higher ratings of nausea and vomiting in the 'obstructed' and 'advanced non-ovarian' groups are unlikely to be mediated by 5HT or 5-HIAA. Ovarian malignancy can cause intermittent, partial or chronic patterns of obstruction, and these may not be sufficiently acute or complete to cause a large release of 5HT, or consequent elevation in 5-HIAA. Lastly, 5HT may act in a paracrine fashion, such that systemic plasma levels were not raised, but subsequent urinary analysis may have shown elevated levels.

Although the emetogenic mechanisms that underlie malignant bowel obstruction may be unclear, our study suggests that systemic 5HT and 5-HIAA did not have a major role in the production of emesis within our sample. Future research studies should be directed at collecting blood and urine samples in early cases of bowel obstruction, and taking serial samples from such patients would allow better analysis of serotonin and its metabolites in this context.

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