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Short Communication

Effects of Ondansetron on Gastrointestinal Symptoms in Carcinoid Syndrome

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The effect of short-term treatment with the highly selective serotonin receptor antagonist ondansetron on symptoms and gastric emptying in 11 carcinoid patients was studied. Diarrhoea improved in 6 of 6 patients, nausea in 3 of 4 patients. Flushing was not affected. The rate of gastric emptying increased during ondansetron treatment ($P = 0.08$). No changes in serotonin in platelets and urinary excretion of 5-hydroxyindoleacetic acid were found. It is concluded that ondansetron can improve gastrointestinal symptoms in carcinoid patients and possibly slows gastric emptying. © **1998 Elsevier Science Ltd. All rights reserved.**

Key words: carcinoid syndrome, ondansetron, diarrhoea, nausea, gastric emptying, applied potential tomography

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INTRODUCTION

CARCINOID TUMOURS are able to produce several bioactive amines, especially serotonin (5-hydroxytryptamine, 5-HT). They cause symptoms such as flushing, diarrhoea, nausea and bronchial obstruction. Reduction of these symptoms may be achieved by inhibition of production or release of serotonin, as well as by interference of its effects. Recently, new selective serotonin receptor antagonists have been developed, providing the opportunity to block the effects of serotonin at specific receptors [1, 2].

In several case reports, 5-HT_3 antagonists have been described as reducing symptoms in carcinoid patients [3–5]. Patients with carcinoid diarrhoea experience several alterations in gut motor function, including an increased postprandial colonic response which can be normalised by ondansetron [6, 7]. Patients may also complain about upper gastrointestinal symptoms. We, therefore, evaluated the effect of the 5-HT_3 receptor antagonist ondansetron in patients with established carcinoid syndrome, examining the incidence of diarrhoea and upper gastrointestinal symptoms and gastric emptying using applied potential tomography (APT).

PATIENTS AND METHODS

11 carcinoid patients (age range 39–68 years) with serotonin overproduction were studied after giving informed consent. None received treatment with somatostatin analogues. 1 patient received recombinant interferon-α, which was continued unaltered while on study. Previous surgery of the stomach was not allowed, nor was medication that could influence gastric motility.

The patients took 8 mg ondansetron (Zofran®, Glaxo, Ware, U.K.) three times daily orally from days 2 to 8. Before therapy and at day 8, gastrointestinal symptoms were scored using a physician's assessment score (0 = no complaints; 1 = mild symptoms, 2 = moderate symptoms; 3 = severe symptoms). Patients completed a visual analogue scale (VAS) concerning their complaints, by drawing a cross on a line between 0 and 10, in which 0 = 'no complaints' and 10 = 'worst possible' [8]. At the end of the treatment, patients completed a VAS concerning the efficacy of ondansetron, in which 0 = 'no effect at all', and 10 = 'very effective'. Before therapy and on day 8, the gastric emptying of 400 ml of meat soup was analysed by APT, after 12 h of fasting [9]. To prevent changes in resistance of gastric contents due to acid secretion, patients received 400 mg cimetidine (Tagamet®, Smith, Kline and Beecham, Philadelphia, Pennsylvania, U.S.A.) intravenously (i.v.) 30 min before the meal. Gastric emptying was expressed as $T_{1/2}$, which is the time taken for half of the meal to be evacuated from the stomach. Gastric emptying was also measured by APT in 10 healthy volunteers (age range 18–27 years) at two different times.

On days 1 and 8, urinary 24-h excretion of serotonin and 5-hydroxyindoleacetic acid (5-HIAA) was measured, as were

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serotonin levels in platelet-poor and platelet-rich plasma and in platelets [10].

Statistical analysis was performed by the Wilcoxon matched-pairs signed-ranks test.

RESULTS

All patients had a histologically proven midgut carcinoid, with liver ($n = 8$), *mesenterial* ($n = 2$) or retroperitoneal ($n = 2$) metastases. Initial complaints were diarrhoea ($n = 6$), flushes ($n = 5$), nausea ($n = 4$), dyspnoea ($n = 1$), meteorism ($n = 1$) and bloating ($n = 1$).

All 6 patients with diarrhoea had improvement of diarrhoea. None of 5 patients with flushes experienced an effect of ondansetron. In 3 of 4 patients nausea improved. In 2 of them, the gastric half emptying time was unchanged, in the third it increased from 8 to 15 min.

8 patients were evaluable for the VAS. At day 1, 4 patients reported no complaints and this was unchanged at day 8. The others put a cross on 2 ($n = 2$) or 4 ($n = 2$); at day 8 they scored 1 ($n = 1$), 2 ($n = 1$), 3 ($n = 1$) and 4 ($n = 1$). On the VAS concerning efficacy, 5 patients scored 0, meaning no effect. 2 patients with improved diarrhoea scored 4. 1 patient with ameliorated diarrhoea scored 7, despite reporting three side-effects (abdominal pain, meteorism and tiredness).

The initial mean gastric half emptying time was 16 min (range 8–29 min, standard error of the mean (SEM) 2 min), which was not significantly different ($P = 0.26$) from the healthy volunteers (20 min, range 9–40 min, SEM 2 min). It increased after ondansetron to 20 min (range 8–42 min, SE 3 min; $P = 0.08$ compared with pretreatment). During treatment, the rate of gastric emptying decreased in 7 patients, increased in 2 patients, and did not change in 2 patients.

Ondansetron induced no changes in the biochemical parameters of serotonin metabolism and caused no substantial side-effects.

DISCUSSION

Diarrhoea in carcinoid patients is thought to be due to high serotonin levels which influence gut motility through specific receptors [11]. There are seven classes and several subclasses of these receptors. Their clinical relevance has not yet been completely elucidated [1, 2].

5-HT_1 and 5-HT_2 receptor antagonists, such as methysergide, cyproheptadine and ketanserin, have benefited some carcinoid patients [12]. Recently, data on 5-HT_3 receptor antagonists in this setting have been reported [3–5, 12]. In this study, we found a symptomatic improvement during ondansetron treatment with respect to diarrhoea and nausea. Flushing was not affected, possibly due to the equivocal relationship between flushing and serotonin levels [11]. As expected, the improvement was not caused by changes in serotonin metabolism, as ondansetron only blocks 5-HT_3 receptors, without influencing serotonin release.

Gastric emptying was slightly faster in patients than in controls in this study. Approximately one-third of patients experienced nausea and in most of them this improved during ondansetron treatment. Whereas a therapeutic effect on nausea is often associated with an increase in the rate of gastric emptying, our results did not show this and even suggest the opposite, possibly due to direct or indirect effects of ondansetron on the stomach and small intestine. Apart from the relatively small number of subjects in this study, the variation of serotonin excretion in carcinoid patients in time is also probably a reason that this finding did not reach significance.

Akkermans and colleagues found that the 5-HT_3 receptor antagonist ICS 205-930 accelerated gastric emptying in normal subjects [13]. Thus, the effects in healthy subjects and in patients with high serotonin levels seem to be opposite. These contradictory effects may be caused by the fact that ICS 205-930, besides its 5-HT_3 blocking activity, also has weak 5-HT_4 receptor antagonist activity, while ondansetron only blocks 5-HT_3 receptors. Another explanation could be the enduring high serotonin levels in patients, possibly causing a down-regulation of the number and/or sensitivity of serotonin receptors.

With more information becoming available about serotonin receptors and their antagonists [1, 2], more specific treatment for symptom relief in patients with a metastatic carcinoid may be possible by combining more selective receptor blockade with currently used general treatment, such as recombinant interferon-α and somatostatin analogues.

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