Pergamon

European Journal of Cancer, Vol. 34, No. 1, pp. 196–198, 1998

Printed in Great Britain
0959-8049/98 $19.00+0.00

PII: S0959-8049(97)00322-5

Short Communication

Urinary 5-Hydroxyindoleacetic Acid (5-HIAA) Excretion During Multiple-day High-dose Chemotherapy

R.J. Janes,[1] T. Muhonen,[1] U.P. Karjalainen[2] and T. Wiklund[1]

[1]Department of Oncology; and [2]Department of Clinical Chemistry, Helsinki University Hospital, 00290 Helsinki, Finland

Highly emetogenic drugs such as cisplatin induce an increase in the urinary 5-hydroxyindoleacetic acid (5-HIAA) level, the main metabolite of serotonin (5-HT), within the first 24 h following a single infusion, thus providing a possible cause for acute emesis and an explanation for the action of 5-HT3 antagonists. No further excretion peaks have been observed, suggesting that additional or serotonin-independent mechanisms cause delayed emesis. Our aim was to study the mechanisms behind emesis seen during a highly emetogenic chemotherapy regimen given as a continuous infusion over several days. Seven women treated with a 4-day high-dose chemotherapy (HDCT) regimen for breast cancer entered the study. Pooled urine samples were collected prior to and during chemotherapy for determining 5-HIAA excretion. An excretion peak in the urinary 5-HIAA level was observed within the first 24 h with no further peaks thereafter. Thus, the mechanisms behind the emesis experienced during this highly emetogenic multiple-day chemotherapy regimen from days 2–3 onwards would appear to be at least partially serotonin independent and would not be expected to be completely relieved by 5-HT3 antagonists alone. © **1998 Elsevier Science Ltd.**

Key words: emesis, nausea, vomiting, 5-HIAA, serotonin, type-3 serotonin antagonists, chemotherapy
Eur J Cancer, Vol. 34, No. 1, pp. 196–198, 1998

INTRODUCTION

AN INCREASE in the plasma and urinary levels of 5-HIAA, the main metabolite of serotonin, is seen in the acute phase of vomiting caused by a single-day infusion of highly emetogenic drugs, such as cisplatin [1]. This rise parallels the temporal onset and severity of nausea and vomiting. Following single-day chemotherapy infusions no further excretion peaks have been observed during the delayed phase of emesis, which thus would appear to be serotonin independent [2]. 5-HT3 antagonists are effective in the treatment of the acute phase of vomiting [3], but their effectiveness in the delayed phase remains to be proven [4].

It is not known whether the mechanism behind emesis seen during a multiple-day chemotherapy regimen is serotonin dependent, caused by continuous or cyclic serotonin excretion. Therefore, we studied the effect of a highly emetogenic multiple-day chemotherapy regimen on the urinary excretion of 5-HIAA.

Correspondence to R. J. Janes.
Received 23 Jan. 1997; revised 28 May 1997; accepted 23 Jun. 1997.

PATIENTS AND METHODS

Seven women (aged 34–58 years, median 49 years) undergoing high-dose chemotherapy (HDCT) for local ($n = 5$) or metastatic ($n = 2$) breast cancer entered this study. Prior to HDCT, the patients had received 3–7 standard cycles of chemotherapy (cyclophosphamide, epirubicin, 5-fluorouracil). Informed consent was obtained from the patients and the study protocol was accepted by the institutional review board.

6 patients received CTCb HDCT and 1 patient received Mitox-CTCb. The CTCb regimen consisted of cyclophosphamide 6 g/m^2, thiotepa 500 mg/m^2 and carboplatinum 800 mg/m^2 given as continuous infusions over 96 h. In the Mitox-CTCb regimen, mitoxantrone 15 mg/m^2 administered over 4 h replaced thiotepa on days 1 and 2. The drugs were infused via separate catheter lumens and the patients received standard hydration.

The anti-emetic regimen contained intravenous ondansetron 8–16 mg and dexamethasone 10–20 mg daily. Lorazepam was given 1–3 mg per day orally or intravenously.

Urine samples for analysing 5-HIAA were collected starting 12 h prior to chemotherapy. Prior, during and after

chemotherapy, pooled urine samples were collected at the following hours: −12–0, 0–3, 3–6, 6–9, 9–12, 12–15, 15–21 and every 12 h thereafter up to either 96 h ($n = 4$) or 144 h ($n = 3$) from the beginning of chemotherapy (= 0 h). 5-HIAA values were determined using HPLL chromatography.

RESULTS

Urinary 5-HIAA excretion was determined starting 12 h before the onset of chemotherapy ($n = 6$), during the 4-day course of chemotherapy ($n = 7$) and for 2 days after discontinuing chemotherapy ($n = 3$). The results are summarised for all 7 patients in Figure 1.

The median baseline 5-HIAA excretion rate during the 12 h prior to chemotherapy was 1.04 μmol/h (range 0.75–1.50). During the 24 h following the initiation of chemotherapy, the median urinary 5-HIAA excretion rate was 1.89 μmol/h (range 1.17–2.38), which was 1.5 times higher than the median urinary excretion rate during the following days. When compared with baseline (−12–0), the median 5-HIAA excretion rate was significantly increased during the first 24 h ($P = 0.006$), the 24–72 h period ($P = 0.009$) and the 72–110 hour period ($P = 0.015$) (paired t-test).

The median peak excretion rate of 5-HIAA, which occurred in the 3–6 h period from the start of chemotherapy, was 4.67 μmol/h (range 3.00–5.67). The urinary 5-HIAA excretion peak took place during the first 24 h in 6 out of the 7 patients; 1 patient presented with two peaks, the first occurring in the 12–15 h period (3.00 μmol/h) and the second at 69 h (3.67 μmol/h).

The 5-HIAA excretion rate of the patient who received the Mitox-CTCb regimen was similar to the excretion seen after the CTCb regimen.

The patients did not experience nausea or vomiting during the 24 h prior to chemotherapy. None of the patients vomited during day 1. More than two emetic episodes were seen in 1/7 patients on day 2, 2/7 on day 3, 4/7 on days 4, 5 and 6.

DISCUSSION

Patients rate nausea and vomiting among the most distressing symptoms caused by chemotherapy [5]. In recent years progress has been made in understanding the mechanisms underlying chemotherapy-induced emesis. Studies looking into serotonin metabolism [6] and work done with selective serotonin type-3 antagonists [7] have elucidated the role of serotonin in the acute phase of chemotherapy-induced emesis. Highly emetogenic drugs, such as high-dose cisplatin [1–3] and dacarbazine [1], produce a marked increase in the plasma and urinary levels of 5-HIAA within the 24 h following infusion of the drug. These rises parallel the temporal onset and severity of vomiting. It is suggested that the mechanism behind the efficacy of specific 5-HT3 antagonists in treating acute nausea and vomiting is their ability to block the central vomiting zone or intestinal chemoreceptors. Serotonin is liberated from the gut's enterochromaffin cells due to chemotherapy-induced damage [6].

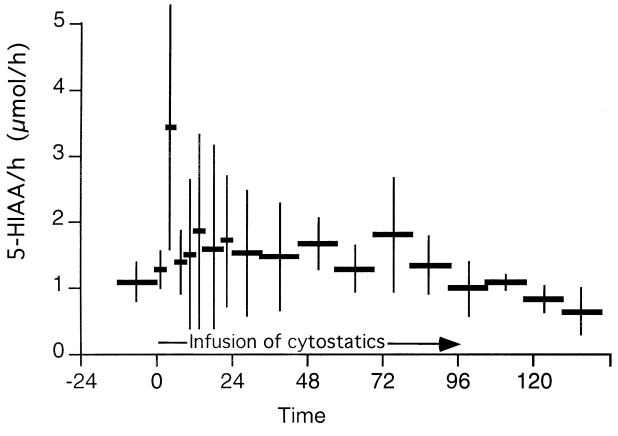

Figure 1. The median 5-HIAA excretion prior, during and after the 4-day course of chemotherapy.

The mechanisms behind delayed emesis are less well understood and the anti-emetic control remains unsatisfactory [8]. Wilder-Smith and associates measured urinary 5-HIAA excretion during the 48 h following high-dose cisplatin 80 mg/m^2 [2]. They found a significant urinary 5-HIAA peak 6 h after the induction of chemotherapy with no peaks thereafter, suggesting that the delayed-phase nausea and vomiting is not associated with the liberation of serotonin. This is supported by the clinical evidence that 5-HT3 antagonists fail to control delayed emesis satisfactorily [4].

In this study we observed a significant increase in the urinary 5-HIAA excretion during the first 24 h following the initiation of a 4-day chemotherapy regimen. The anti-emetic control was good at the beginning of the 4-day course of chemotherapy, coinciding with the increased urinary excretion of 5-HIAA. This is consistent with the reported good anti-emetic control achieved using a combination of a 5-HT3 antagonist and dexamethasone in treating serotonin-induced emesis [9]. From day 4 onwards, the anti-emetic treatment failed to control emesis in 4 of the 7 patients. Neither 5-HT3 antagonists nor dexamethasone affect the release of serotonin [10].

It seems that the initial emptying of serotonin reserves from the intestinal mucosa induced by the initiation of chemotherapy is not followed by further significant excretion peaks despite the continuing chemotherapy stimulation. Thus, the mechanisms behind emesis seen during highly emetogenic multiple-day chemotherapy from days 2–3 onwards would appear to be at least partially serotonin independent and would not be expected to be fully relieved by 5-HT3 antagonists alone.

1. Cubeddu LX, Hoffman IS, Fuenmayor NT, Malave JJ. Changes in serotonin metabolism in cancer patients: its relationship to nausea and vomiting induced by chemotherapeutic drugs. *Br J Cancer* 1992, **66**, 198–203.
2. Wilder-Smith OHG, Borgeat A, Chappuis P, Fathi M, Forni M. Urinary serotonin metabolite excretion during cisplatin chemotherapy. *Cancer* 1993, **72**, 2239–2241.
3. Cubeddu LX, Hoffman IS, Fuenmayor NT, Finn AL. Efficacy of ondansetron (GR 38032F) and the role of serotonin in cisplatin-induced nausea and vomiting. *N Engl J Med* 1990, **322**, 810–816.
4. Roila F, De Angelis V, Contu A, *et al.* Ondansetron (OND) vs metoclopramide (MTC) both combined with dexamethasone (DEX) in the prevention of cisplatin (CDDP)-induced delayed emesis. *Proc Am Soc Clin Oncol* 1996, **15**, 1705 (abstract).
5. Coates A, Abraham S, Kaye SB, *et al.* On the receiving end—patient perception of the side-effects of cancer chemotherapy. *Eur J Cancer Clin Oncol* 1983, **19**, 203–208.
6. Cubeddu LX. Mechanisms by which cancer chemotherapeutic drugs induce emesis. *Semin Oncol* 1992, **19**(S15), 2–13.
7. Hesketh PJ. Treatment of chemotherapy-induced emesis in the 1990s: impact of the 5-HT3 receptor antagonists. *Support Care Cancer* 1994, **2**, 286–292.
8. Kris MG, Pisters KMW, Hinkley L. Delayed emesis following anticancer chemotherapy. *Support Care Cancer* 1994, **2**, 297–300.

9. Roila F, Tonato M, Cognetti F, *et al.* Prevention of cisplatin-induced emesis: a double-blind multicenter randomized cross-over study comparing ondansetron and ondansetron plus dexamethasone. *J Clin Oncol* 1991, **9**, 675–678.

10. Cubeddu LX, O'Connor DT, Parmer RJ. Plasma chromogranin A: a marker of serotonin release and of emesis associated with cisplatin chemotherapy. *J Clin Oncol* 1995, **13**, 681–687.