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Serotonin metabolism following platinum-based chemotherapy combined with the serotonin type-3 antagonist tropisetron

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Abstract The administration of platinum-based chemotherapy induces serotonin release from the enterochromaffin cells, causing nausea and vomiting. This study was conducted to evaluate parameters of serotonin metabolism following platinum-based chemotherapy given in combination with the serotonin type-3 antagonist tropisetron as an antiemetic agent. In nine chemotherapy-naive patients with disseminated germ-cell tumors, parameters of serotonin metabolism in both blood and urine were evaluated during two consecutive courses of platinum-based chemotherapy. Serotonin concentrations in platelet-rich plasma and platelet-poor plasma as well as urinary 5-hydroxyindoleacetic acid (5-HIAA) and serotonin levels were measured during the full length of the courses. By means of comparison with the antiemetic agent chlorpromazine, used on day 1 of the first course only, the effect of the serotonin type-3 antagonist tropisetron, the antiemetic agent used during the rest of the courses, on these parameters was studied. Clinical effects were also recorded. No change in the parameters of serotonin metabolism could be demonstrated during either course by the serotonin type-3 antagonist tropisetron. Also in vitro, no effect of tropisetron on the active serotonin uptake by platelets was found. Serotonin levels in platelets showed no correlation with emetic response. However, the platelet serotonin content decreased significantly between the first and the second course ($P < 0.01$). The significant reduction in platelet serotonin content observed between the first and the second course indicates a depletion of total body serotonin. The role of a serotonin type-3 antagonist might be affected by the altered serotonin equilibrium during later courses of chemotherapy.

Key words Serotonin metabolism · Serotonin type-3 antagonist

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Introduction

Nausea and vomiting are frequent and distressing side effects of chemotherapy, especially of treatment with platinum compounds [11,12,15]. The administration of platinum-based chemotherapy is thought to induce serotonin release from the enterochromaffin cells of the gastrointestinal tract. Platinum compounds induce an increased serotonin metabolism in cancer patients [6,24] and an increased release of serotonin from animal ileal tissue [17]. If released, high concentrations of serotonin within the gut wall could activate serotonin type-3 receptors on vagal afferents and, subsequently, the vomiting center. It could be speculated that also by entering the portal circulation and thus activating the vomiting center, serotonin might induce nausea and vomiting [7,23]. The observation that selective serotonin type-3 antagonists considerably reduce chemotherapy-induced acute nausea and vomiting as compared with other antiemetic agents [5,16] supports a key role of serotonin in chemotherapy-induced nausea and vomiting.

Serotonin has a physiological role in controlling gastrointestinal motility. Approximately 80% of the total-body serotonin content is stored in the enterochromaffin cells [2,7]. A number of mechanisms have evolved to clear released serotonin rapidly from the circulation. Serotonin is metabolized in the endothelial cells of the lungs and liver to 5-hydroxyindoleacetic

acid (5-HIAA), which is subsequently excreted in the urine [10]. Furthermore, serotonin is actively taken up by platelets; this may be referred to as the "scavenger" role of platelets [20]. As compared with the aforementioned inactivation in the liver and lung, serotonin uptake by platelets is a relatively slow process. However, increased plasma levels of free circulating serotonin may result in increased platelet serotonin levels [13]. In the circulation, serotonin is almost entirely confined to platelets.

This study was conducted to evaluate parameters of serotonin metabolism following platinum-based chemotherapy given in combination with the serotonin type-3 antagonist tropisetron. During the full length of two consecutive courses of chemotherapy, serotonin concentrations in platelet-rich plasma and platelet-poor plasma as well as urinary 5-HIAA and serotonin levels were measured. The effect of tropisetron on these parameters was studied as well as its clinical effect. The effect of tropisetron on serotonin uptake by platelets was established in vitro. Serotonin metabolism following platinum-based chemotherapy has not been studied in this setting before.

Patients and methods

Patients

Nine patients with a histologically confirmed germ-cell tumor, scheduled to be treated with platinum-containing chemotherapy according to European Organization for Research and Treatment of Cancer (EORTC) protocol 30896 and 18 years of age or older, were entered in the study. Patients were excluded if they had a current or relevant history of a medical condition that could either interfere with the evaluation of the study medication or put the patient at risk, e.g., insufficiently controlled hypertension; severe hepatic, renal, or cardiac insufficiency; uncontrolled infection; drug or alcohol abuse; or hypersensitivity reactions or drug allergy. Informed consent was obtained from all patients, and the study was approved by the Medical Ethics Committee of the University Hospital, Groningen, The Netherlands.

Medication

Cisplatin dissolved in 1 l 0.9% NaCl was given i.v. at 20 mg/m^2 per day for 5 consecutive days to seven patients. Further treatment consisted of infusions of bleomycin given at 30 mg in 1 l 0.9% NaCl on day 2 and of etoposide given at 120 mg/m^2 per day in 0.9% NaCl on days 1–3. Patients received prophylactic antiemetic treatment before cisplatin administration on days 1–6. Chlorpromazine was infused i.v. at 15 mg over 15 min before and after the cisplatin infusion on day 1 of the first course. On days 2–6, a 5-mg tropisetron capsule was given orally each day. On day 21 (day 1 of the second course), 5 mg tropisetron was infused i.v. over 15 min. On days 2–6 of the second course, a 5-mg tropisetron capsule was given orally each day. In both courses, tropisetron was given 30 min before the cisplatin infusion.

Carboplatin at $\geq$ 400 mg/m^2 per day (the dose depended on renal function) was given i.v. in 500 ml 5% glucose to two patients on day 1. Further treatment consisted of infusions of bleomycin given at 30 mg in 500 ml 0.9% NaCl on day 2 and of etoposide given at 120 mg/m^2 per day in 0.9% NaCl on days 1–3. Patients received prophylactic antiemetic treatment before chemotherapy on days 1–3. Chlorpromazine at 15 mg was infused i.v. over 15 min before and after the carboplatin infusion on day 1 of the first course. On days 2 and 3, a 5-mg tropisetron capsule was given once daily. On day 21 (day 1 of the second course), 5 mg tropisetron was infused i.v. over 15 min. On days 2 and 3 of the second course, a 5-mg tropisetron capsule was given daily. In both courses, tropisetron was given 30 min before the carboplatin infusion. Tropisetron for this study was kindly supplied by Sandoz (Basel, Switzerland).

Antiemetic response

At each blood and urine sampling time, nausea and vomiting were scored. The number of emetic episodes were recorded. Patients were asked to categorize the effect of nausea on their daily activities either as not disturbing or as (very) disturbing. The overall response criteria for nausea and vomiting were: complete response – no emetic episodes, no disturbing nausea; major response — 0–2 emetic episodes, nausea not disturbing; minor response — 2–5 emetic episodes, nausea disturbing; failure — more than 5 emetic episodes, nausea very disturbing.

Samples

Blood samples were obtained from cisplatin-treated patients on day 1 at 30 min prior to the cisplatin infusion (before administration of the antiemetic agent), at 1 h after the start of the cisplatin infusion, and after 4 h (at the end of the infusion) and 16 h (on day 2). Blood samples were also obtained on day 5 (after the last cisplatin administration) and on day 8. Blood samples were obtained from carboplatin-treated patients on day 1 at 30 min prior to the carboplatin infusion (before administration of the antiemetic agent), at 1 h after the start of the carboplatin infusion, and after 1.5 h (at the end of the infusion) and 4 h. Blood samples were also obtained after 16 h (on day 2) and on day 3. Each time, a sample of 10 ml blood was drawn by venipuncture or through an i.v. line separate from the chemotherapy-administration system into a chilled tube containing 0.12 ml ethylenediaminetetraacetate (EDTA). Blood samples were centrifuged for 30 min at 120 *g* and 4°C. Platelet-rich plasma was separated into platelet-poor plasma and a pellet by centrifugation for 30 min at 800 *g* and 4°C. $Na_2S_2O_5$ and EDTA were added as preservatives to a final concentration of about 10 g/l each.

Urine samples were collected (at the same time as the blood samples) into 125-ml plastic cups. $Na_2S_2O_5$ and EDTA were added as preservatives to a final concentration of about 10 g/l each. Samples were acidified to a pH of 4 with acetic acid prior to freezing.

Analytical methods

Serotonin contents of platelet-rich plasma, platelet-poor plasma, and urine were determined using high-performance liquid chromatography with fluorometric detection as described by Kwarts et al. [14]. Platelet concentrations in whole blood and platelet-rich plasma were measured with a Coulter counter model S plus 4 (Coulter Electronics, Hialeah, Fla. USA). The platelet serotonin content, expressed in nanomoles of serotonin per 10^9 platelets, was calculated by dividing the concentration of serotonin in platelet-rich plasma by its platelet concentration. The total load of serotonin in platelets in blood (nanomoles of serotonin in platelets per liter of blood) was then calculated by multiplying the platelet serotonin content with the number of platelets per liter of whole blood. The analytical detection limit for plasma serotonin concentration was 0.5 mol/l. Urinary 5-HIAA concentrations were deter-

mined in ether extracts of 1 ml urine using high-performance liquid chromatography with fluorometric detection essentially as described by Rosano et al. [21]. Urinary creatinine levels were measured by a picric acid method on an SMA-2 analyzer (Technicon Instruments, Tarrytown, N.Y., USA). The analytical detection limit for urinary 5-HIAA concentration was approximately 0.05 mmol/mol creatinine (0.1 pmol on the column), depending on the urinary creatinine content. Urinary 5-HIAA concentrations, expressed in millimoles per mole of creatinine, were calculated by dividing the concentration of 5-HIAA by its creatinine concentration.

In vitro experiment

From healthy volunteers, blood was drawn by venipuncture into a 10-ml tube containing 0.12 ml EDTA. After a whole-blood platelet count had been performed, platelet-rich plasma was prepared and a platelet count, again performed. Plastic tubes with 1 ml platelet-rich plasma were incubated with 500 ng serotonin plus or minus 15–150 ng tropisetron. Tropisetron and serotonin were dissolved in 50 µl 0.9% NaCl each. Serotonin at this concentration would not surpass the active uptake capacity of platelets [11], and tropisetron at 15 ng would equate with the blood plasma level observed after a 5-mg dose, conforming to the in vivo situation in this study (investigators' brochure). Samples were preincubated with tropisetron for 10 min at 37°C, after which serotonin was added and samples were incubated for 60 min at 37°C. From each tube, 500 µl platelet-rich plasma was used for serotonin determination. The rest of the tube content was used for preparing platelet-poor plasma, in which serotonin was also measured, as described above. This experiment was repeated three times with different volunteers.

Statistical analysis

The Wilcoxon matched-pairs signed-rank test was used to compare serotonin and 5-HIAA levels in samples from course one with those in course-two samples. The same test was used to relate serotonin levels to the baseline. The rank-sum test was used to compare platelet numbers in samples of the first and the second course. A P value below 0.05 was considered to indicate statistical significance.

Results

Antiemetic response

On the 1st day of the first course the acute type of nausea and vomiting (within 24 h after the administration of the cytostatic agent) was controlled completely by chlorpromazine in only one patient of nine. Two patients showed a major response, two patients showed a minor response, and in four patients the treatment failed. During the second course, acute nausea and vomiting was completely controlled by tropisetron in eight patients; one patient showed a major response. Delayed vomiting (after 24 h and within 5 days after the administration of the cytostatic agent) was recorded for cisplatin-treated patients ($n = 7$). In the first course it was completely controlled by tropisetron in three patients; two patients showed a major response and two patients showed a minor response. During the second course (also with tropisetron), no complete response was achieved; five patients showed a major response and two patients showed a minor response.

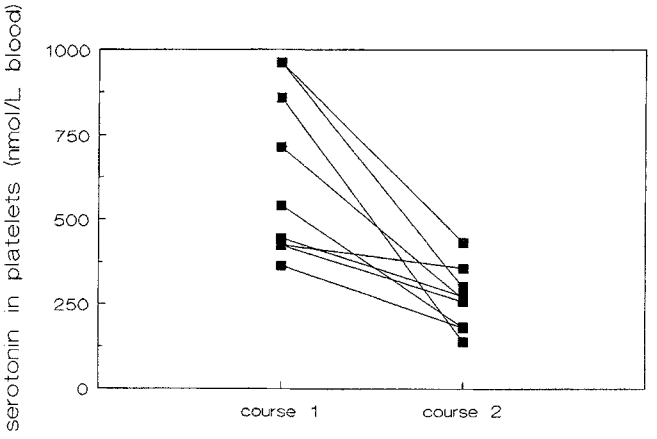

Fig. 1 Serotonin levels in platelets (nmol/l blood; Y-axis) as measured in blood samples obtained before courses 1 and 2

Blood samples

Figure 1 shows the serotonin values obtained in platelets for the individual patients ($n = 9$) before course one and course 2. Total circulating serotonin levels measured in platelets were higher before the first course (median, 542 nmol/l blood; range, 599 nmol/l blood) than before course 2 (median, 266 nmol/l blood; range, 293 nmol/l blood; $P < 0.01$ for matched pairs).

Figure 2 shows the serotonin values measured during courses 1 and 2 in the platelets of cisplatin-treated patients ($n = 7$) . The sampling times and corresponding serotonin levels determined in platelets are presented. The values obtained at the separate sampling times showed no significant difference from the baseline values, either after the administration of cisplatin or during the use of chlorpromazine. This was also the case for the samples obtained on day 5 (tropisetron) and day 8 (no antiemetic agent). In all samples taken from cisplatin-treated patients the serotonin levels measured in platelets during the second course were significantly lower than those measured during the first course ($P = 0.02$) . As found for the first course, the values obtained at the separate sampling times showed no significant difference from the baseline values.

Figure 3 shows the serotonin values measured during courses 1 and 2 in platelet-poor plasma of cisplatin-treated patients ($n = 7$) . The sampling times and corresponding platelet-poor plasma serotonin values are presented. No particular trend in time could be discerned. The serotonin levels measured in platelet-poor plasma during course 1 did not differ significantly from those determined during course 2.

Measurements in carboplatin-treated patients ($n = 2$) are not shown in Figs. 2 and 3 because of the

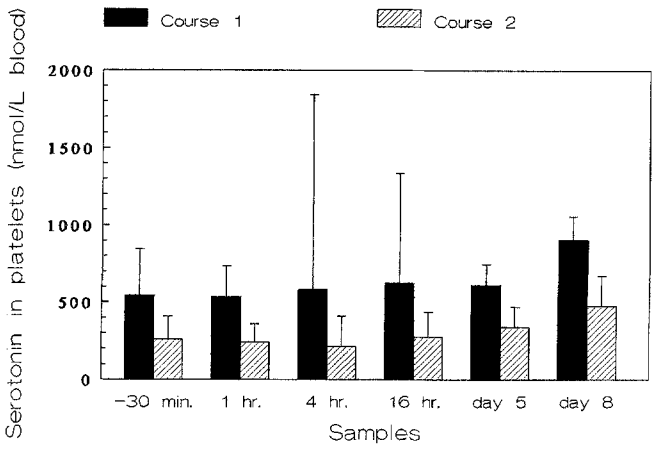

Fig. 2 Sampling times (X-axis) and corresponding serotonin concentrations measured in platelets (nmol/l blood; Y-axis) during courses 1 and 2 in cisplatin-treated patients ($n = 7$; median and half range)

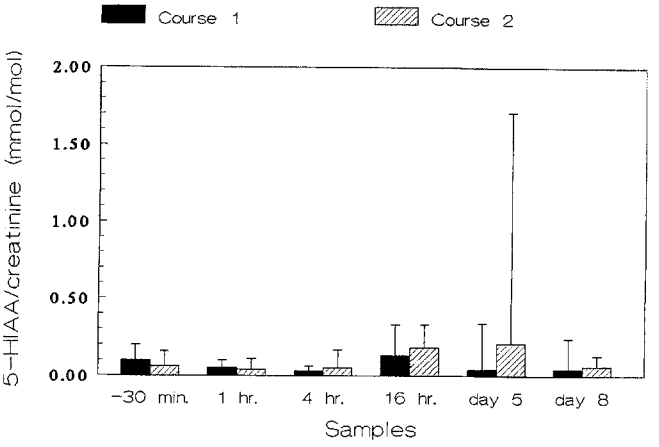

Fig. 4 Sampling times (X-axis) and corresponding urinary 5-HIAA levels (mmol 5-HIAA/mol creatinine; Y-axis) measured during courses 1 and 2 in cisplatin-treated patients ($n = 7$; median and half range)

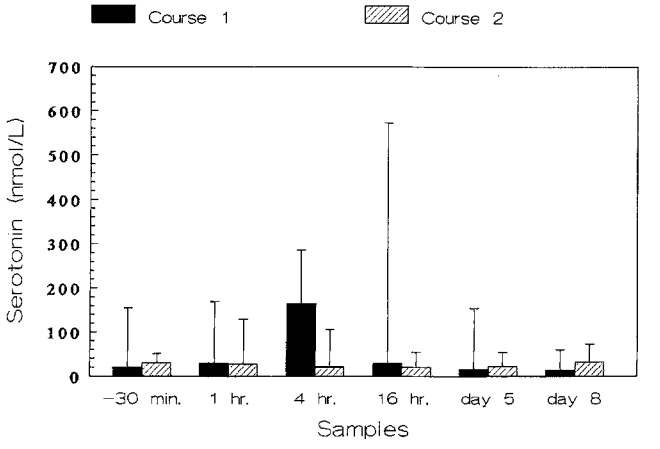

Fig. 3 Sampling times (X-axis) and corresponding plasma serotonin levels (nmol/l platelet-poor plasma; Y-axis) measured during courses 1 and 2 in cisplatin-treated patients ($n = 7$; median and half range)

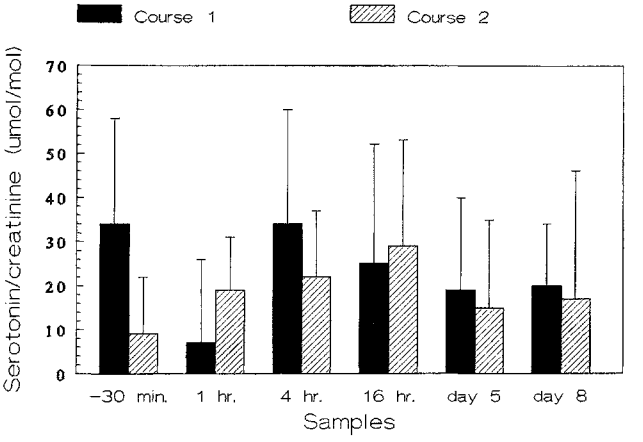

Fig. 5 Sampling times (X-axis) and corresponding urinary serotonin concentrations (μmol serotonin/mol creatinine; Y-axis) measured during courses 1 and 2 in cisplatin-treated patients ($n = 7$; median and half range)

different sampling times. However, in carboplatin-treated patients, trends other than those observed in cisplatin-treated patients were not observed. Platelet counts obtained before the first and the second course were not significantly different. We observed an average decrease of 46% in the platelet count at 15 days after the start of the first course.

Urine samples

Figure 4 shows urinary 5-HIAA levels measured during courses 1 and 2 in cisplatin-treated patients ($n = 7$). In Fig. 5 the urinary serotonin levels determined during courses 1 and 2 in cisplatin-treated patients ($n = 7$) are shown. The urinary 5-HIAA values as well as the serotonin levels determined during either course did not differ significantly from the initial levels of their course. For none of the separate samples could a significant difference between course one and course two be demonstrated. Measurements in carboplatin-treated patients ($n = 2$) are not shown in Figs. 4 and 5 because of the different sampling times. However, in carboplatin-treated patients, trends other than those observed in cisplatin-treated patients were not observed.

Relationship of antiemetic response/platelet serotonin

When the antiemetic response was compared with the serotonin level in platelets of individual patients, no relationship could be distinguished. This was the case for all sampling times during both courses.

In vitro experiment

Serotonin concentrations in platelets, expressed as percentages of the total serotonin count, showed that after incubation with serotonin only, 97.7% ± 1.3% of the total serotonin content was confined to platelets. The value obtained with 15 ng tropisetron and serotonin was 96.7% ± 2.6%, and that obtained with 150 ng tropisetron and serotonin was 97.7% ± 1.3%.

Discussion

Serotonin is thought to play an important role in chemotherapy-induced nausea and vomiting [18]. This study was conducted to evaluate parameters of serotonin metabolism following platinum-based chemotherapy given in combination with the serotonin type-3 antagonist tropisetron as an antiemetic agent. Chemotherapy-naive patients were selected for this study to preclude the possible influence of previous treatment on the parameters investigated.

During course one as well as course two, the serotonin values measured in platelets at comparable sampling times showed no significant difference from the baseline level of their course. This has previously been noted by Cubeddu et al. [6], who measured plasma and platelet serotonin levels over 10 h following high-dose cisplatin administration. In our study, other serotonin-metabolism parameters showed no significant change either. For platelet-poor plasma serotonin, this finding is consistent with the observation of Barnes et al. [1] that following dosing with cisplatin at 20mg/m^2, this parameter rises in only a minority of patients. A rise in urinary 5-HIAA levels following the administration of high-dose cisplatin has been demonstrated in a number of studies [6, 24]. As this rise was shown to be related to the dose of cisplatin [6], an explanation for its absence in our study may be found in the lower dose of cisplatin used by us.

In this study, no difference in the effect of either chlorpromazine or tropisetron on these parameters could be demonstrated. For free circulating serotonin, this finding is consistent with the results of our in vitro study, which showed that the serotonin type-3 antagonist tropisetron has no influence on the active uptake of plasma serotonin by platelets. A difference between chlorpromazine and tropisetron was observed concerning the clinical response to nausea and vomiting, which is consistent with the finding of superior antiemetic efficacy for serotonin type-3 antagonists in acute chemotherapy-induced vomiting and nausea [4, 9, 19]. The difference in the antiemetic response to either tropisetron on chlorpromazine and their lack of effect on the parameters of serotonin metabolism suggest that no relationship exists between antiemetic response and measurable parameters of serotonin metabolism. This was confirmed in our study for the relationship between antiemetic response and serotonin levels in platelets per liter of blood. It has been suggested that chemotherapy-induced emesis is caused mainly by gastrointestinal serotonin instead of circulating serotonin [6]. Our results further support this contention.

The serotonin level in platelets per liter of blood was decreased in the second course as compared with the first course. This was due to a decrease in the platelet serotonin content because platelet counts before the first and the second course were not different. Considering that the bulk of the serotonin content of platelets originates in the enterochromaffin cells of the gastrointestinal tract [22] and that platelets do not have the capacity to synthesize serotonin themselves [8], the platelet serotonin content gives an impression of the serotonin content of the enterochromaffin cells. These results indicate the occurrence of a decrease in body serotonin between the first and the second course of treatment with platinum compounds. A decrease in the antiemetic efficacy of serotonin type-3 antagonists other than tropisetron in consecutive courses has been shown in a number of studies [3, 9]. It is conceivable that the changed body serotonin level observed in the later courses could have an effect on the efficacy of serotonin type-3 antagonists.

The observed decrease in body serotonin content between course one and course two of platinum-based chemotherapy would also likely be reflected in parameters of serotonin metabolism other than the serotonin level in platelets. However, this was not demonstrated in the present study. The lack of a decrease in free serotonin levels from course one to course two might be explained by the rapid removal of circulating serotonin from the plasma as described in the introduction. Urinary excretion of 5-HIAA is mainly derived from serotonin turnover in enterochromaffin cells of the gastrointestinal tract [2]. Therefore, the lack of a decrease in the initial urinary 5-HIAA levels from course one to course two is not consistent with the finding in serotonin levels in platelets. However, a possible explanation could be that during the first course, 5-HIAA levels might have been lowered due to prehydration and may sometimes have fallen below the detection level of the described method. A decrease in 5-HIAA levels in that situation would be impossible to detect.

In conclusion, no change in the parameters of serotonin metabolism could be demonstrated during either course. These parameters were not affected by the serotonin type-3 antagonist tropisetron. The total circulating serotonin levels measured in platelets showed no correlation with the emetic response. However, the platelet serotonin content decreased between the first and the second course, which indicates a depletion of total-body serotonin. The role of a serotonin type-3 antagonist as an antiemetic agent might be affected by the altered serotonin equilibrium during later courses of chemotherapy.

References

1. Barnes NM, Ge J, Jones WG, Naylor RJ, Rudd JA (1990) Cisplatin induced emesis: preliminary results indicative of changes in plasma levels of 5-hydroxytryptamine, Br J Cancer 62: 862
2. Bertaccini G, Chieppa S (1960) Urinary excretion of 5-hydroxyindoleacetic acid after removal of the large intestine in man. Lancet I: 881
3. Blijham GH (1992) Does granisetron remain effective over multiple cycles? Eur J Cancer 28A [Suppl]: 17
4. Bruntsch U, Drechsler S, Hiller E, Eiermann W, Tulusan AH, Buhner M, Hartenstein R, Koenig HJ, Gallmeier WM (1992) Prevention of chemotherapy-induced nausea and emesis in patients responding poorly to previous antiemetic therapy: comparing tropisetron with optimised standard antiemetic therapy. Drugs 43 [Suppl 3] : 23
5. Cubeddu LX, Hoffmann IS, Fuenmayor NT, Finn AL (1990) Efficacy of ondansetron (GR 38032F) and the role of serotonin in cisplatin-induced nausea and vomiting. N Engl J Med 322: 810
6. Cubeddu LX, Hoffmann IS, Fuenmayor NT, Malave JJ (1992) Changes in serotonin metabolism in cancer patients: its relationship to nausea and vomiting induced by chemotherapeutic drugs. Br J Cancer 66: 198
7. Farthing MJG (1991) 5-Hydroxytryptamine and 5-hydroxytryptamine-3 receptor antagonists. Scand J Gastroenterol 26 [Suppl 188] : 92
8. Fuller RW, Wong DT (1990) Serotonin uptake and serotonin uptake inhibition. Ann NY Acad Sci 600: 68
9. Gandara DR (1991) Progress in the control of acute and delayed emesis induced by cisplatin. Eur J Cancer 27 [Suppl]: 9
10. Gillis CN (1985) Peripheral metabolism of serotonin. In: VanHoutte PM (ed) Serotonin and the cardiovascular system. Raven Press, New York, p 27
11. Gralla RJ (1983) Metoclopramide: a review of antiemetic trials. Drugs 25 [Suppl 1]: 63
12. Gralla RJ, Itri LM, Pisko SE, Squillante AE, Kelsen DP, Braun DW Jr, Bordin LA, Braun TJ, Young CW (1981) Antiemetic efficacy of high-dose metoclopramide: randomized trials with placebo and prochlorperazine in patients with chemotherapy induced nausea and vomiting. N Engl J Med 305: 905
13. Kema IP, De Vries EGE, Schellings AMJ, Postmus PE, Muskiet FAJ (1992) Improved diagnosis of carcinoid tumors by measurement of platelet serotonin. Clin Chem 38: 534
14. Kwarts E, Kwarts J, Rutgers H (1984) A simple paired-ion liquid chromatography assay for serotonin in cerebrospinal fluid, platelet rich plasma, serum and urine. Ann Clin Biochem 21: 425
15. Laszlo J (1983) Nausea and vomiting as major complications of cancer chemotherapy. Drugs 25 [Suppl 1]: 1
16. Marty M, Pouillart P, Scholl S, Droz JP, Azab M, Brion N, Pujade-Lauraine E, Paule B, Paes D, Bons J (1990) Comparison of the 5-hydroxytryptamine-3 (serotonin) antagonist ondansetron (GR 38032F) with high-dose metoclopramide in the control of cisplatin induced emesis. N Engl J Med 322: 816
17. Milano S, Simon C, Grelot L (1991) In vitro release and tissue levels of ileal serotonin after cisplatin-induced emesis in the cat. Clin Auton Res 1: 275
18. Miner WD, Sanger GJ, Turner DH (1987) Evidence that 5-HT_3 receptors mediate cytotoxic drug and radiation-evoked emesis. Br J Cancer 56: 159
19. Mulder PHM de, Seynaeve C, Vermorken JB, Van Liessum PA, Mols-Jevdevic S, Allman EL, Beranek P, Verweij J (1990) Ondansetron compared with high-dose metoclopramide in the prophylaxis of acute and delayed cisplatin-induced nausea and vomiting. Ann Intern Med 113: 834
20. Pletscher A (1987) The hydroxytryptamine system of blood platelets: physiology and pathophysiology. Int J Cardiol 14: 177
21. Rosano TG, Meola JM, Swift TA (1992) Liquid-chromatographic determination of urinary 5-hydroxy-3-indoleacetic acid, with fluorescence detection. Clin Chem 28: 207
22. Stolz JF (1985) Uptake and storage of serotonin by platelets. In: VanHoutte PM (ed) Serotonin and the cardiovascular system. Raven Press, New York, p 37
23. Talley NJ (1992) 5-Hydroxytryptamine agonists and antagonists in the modulation of gastrointestinal motility and sensation: clinical implications (review). Aliment Pharmacol Ther 6: 273
24. Wilder-Smith OHG, Borgeat A, Chappuis P, Fathi M, Forni M (1993) Urinary serotonin metabolite excretion during cisplatin chemotherapy. Cancer 72: 2239