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ORIGINAL ARTICLE

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Possible cardiac side effects of granisetron, an antiemetic agent, in patients with bone and soft-tissue sarcomas receiving cytotoxic chemotherapy

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Abstract The cardiac effect of granisetron, a selective 5-hydroxytryptamine$_3$ receptor antagonist, on 12 patients with bone and soft-tissue sarcomas treated by cytotoxic chemotherapy consisting of multiple courses was examined. Of the 12 patients, 4 showed significant electrocardiographical changes, including sinus bradycardia, integral change of P-waves, junctional escape beat, and atrioventricular (AV) block with Wenckebach phenomenon, indicating stimulatory regulation of the vagus nerve. These changes were observed in each patient after several courses of chemotherapy but not in the first course. There was no correlation between the electrocardiographical changes and the chemotherapeutic agents used or the type of tumor present. A patient with osteosarcoma showed persistent bradycardia in three courses, all protocols of which contained high-dose methotrexate. From these findings we conclude that the cardiac responses may be due to stimulated activity of the vagal efferent nerve, which is regulated reflexly by afferent nerve activity suppressed by granisetron. On the other hand, the antiemetic efficacy of granisetron was satisfactory. These results suggest that careful observation of the heart is necessary when granisetron is used, especially for chemotherapy consisting of repeated multiple courses.

Key words Antiemetics · Granisetron · Chemotherapy · Arrhythmia · Vagus nerve

Introduction

The introduction of new anti-cancer agents and supportive measures has improved the prognosis of bone and soft-tissue sarcoma. However, nausea and vomiting remain distressing side effects of chemotherapy regimens [6]. Thus, control of these complaints is essential for the patient's survival since serious nausea and vomiting result in depressed nutritional intake, serious metabolic derangement, and finally rejection by the patient of a potentially effective treatment [9].

Granisetron, which is a selective 5-hydroxytryptamine$_3$ 5-HT$_3$ receptor antagonist, has recently been shown to be a strong antiemetic agent for cytotoxic chemotherapy and irradiation [4,14,16]. Adverse events previously reported in most cases have been headache, diarrhea, or constipation [1,17]. On the other hand, it has been proposed that the sites of action of granisetron at 5-HT$_3$ receptors are located on vagal afferent fiber terminals [15,19]. It is thus important that careful examination of the effect on the heart be performed, since this system is under the control of the vagus nerve. In the present communication, we describe the effects on the heart observed in patients with bone and soft tissue sarcomas who were treated with adjuvant chemotherapy. Although our results conflict with those reported by Upward et al. [25] who found no important effect on cardiovascular parameters, including the pulse rate and ECG in healthy volunteers, we conclude that cardiac reactions may be induced by granisetron from both the clinical and the pharmacokinetic point of view.

Patients and methods

Patients

A total of 72 patients who were attending the Gunma University hospital between June 1992, when granisetron was introduced to the hospital, and June 1993 for the treatment of bone and soft-tissue sarcoma were studied. Of these 12 patients, 11 were male. Their mean age was 22.8 (range 7–52) years and their mean body weight 51, (range, 24.5–76) kg. Four patients previously had one or more courses of chemotherapy with other antiemetic agents including

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metoclopramide, diazepam, and methylprednisolone sodium succinate. Patients were excluded from the study if they had marked hepatic dysfunction, renal dysfunction, or active peptic ulcer. At less than 2 weeks before each course of chemotherapy, no abnormality was noted on the electrocardiographical (ECG) examination in any of the patients presented herein. Four of the patients had osteosarcoma (OS), four had rhabdomyosarcoma, three had malignant fibrous histiocytoma (MFH), and one had Ewing's sarcoma.

Cytotoxic chemotherapy regimens

Patients with OS were treated with neoadjuvant chemotherapy according to the protocol described by Bacci et al. [5] or the T-10 protocol described by Rosen et al. (23). These sequential protocols consisted of high-dose methotrexate (MTX), vincristine (VCR), cisplatin (CDP), a doxorubicin derivative, pirarubicin (THP), and bleomycin (BCD). Patients with MFH, rhabdomyosarcoma, and Ewing's sarcoma received T-9 adjuvant chemotherapy, consisting of a cyclophosphamide derivative, ifosfamide (IFM), THP, MTX, VCR, BCD, and actinomycin D (ACD) instead of dactinomycin (22). Each patient received a mean of 5.9 (range, 2–14) courses.

Antiemetic treatment and evaluation of the effect on cardiovascular parameters

Granisetron (SmithKlein-Beecham Pharmaceuticals Co., Ltd) was given at a prophylactic dose of 50 μg/kg as a 10-min intravenous infusion at 1 h before the start of the administration of chemotherapeutic drugs. The pulse rate and blood pressure were checked every hour on this day and four times per day for the next several days. Continuous ECG monitoring was performed beginning 1 h before the administration of granisetron for 5 days. Holter ECG monitoring was performed in a patient with OS to examine the dynamic daily changes in his ECG.

Results

Cardiac effect shown on ECG monitoring

As shown in Table 1, 4 of 12 patients showed significant ECG changes in 12 of a total of 72 courses. All of these patients received more than nine courses, and the changes were detected after several repetitions of the chemotherapy but not in the first course of the treatment. These ECG changes correlated with neither the chemotherapeutic agents used nor the type of tumor. In the ECG monitoring study, sinus bradycardia was noted in patients 1, 3, and 4 (Fig. 1). There were integral changes in P-waves and junctional escape beat in cases 3 and 4, respectively, which can be assumed to be due to autonomic secondary pacemakers induced by the suppression of normal rhythmic sinus-node activity (Fig. 1). An increase in the atrioventricular (AV) conduction time was another evident change in the ECG.

Table 1 Chemotherapeutic courses with ECG changes (*MTX* Methotrexate, *VCR* vincristine, *BCD* bleomycin, *ACD* actinomycin D, *IFM* ifosfamide, *THP*, pirarubicin; *CDP*, cisplatin

Patient		Chemotherapy course		Persistent bradycardia[a]
Age (years)	Tumor type	Number from the first course in each patient	Regimens per course	
Case 1				
17	Osteosarcoma	9th	High-dose MTX, VCR	
		10th	High-dose MTX,VCR	+
		11th	High-dose MTX, VCR	+
		13th	VCR, BCD, ACD, IFM	
		14th	High-dose MTX, VCR	+
		15th	THP, IFM	
Case 2				
23	Malignant fibrous histiocytoma	10th	THP, MTX, IFM	
		11th	VCR, THP, MTX, IFM	
Case 3				
11	Osteosarcoma	7th	High-dose MTX, VCR	
		8th	THP, CDP	
Case 4				
7	Rhabdomyosarcoma	6th	THP, CDP	
		7th	VCR, BCD, ACD, IFM	

[a] Persistent bradycardia is designated as a continuously suppressed pulse rate lasting for 2 days, including episodes of less than 50 beats per minute persisting for at least 5 min

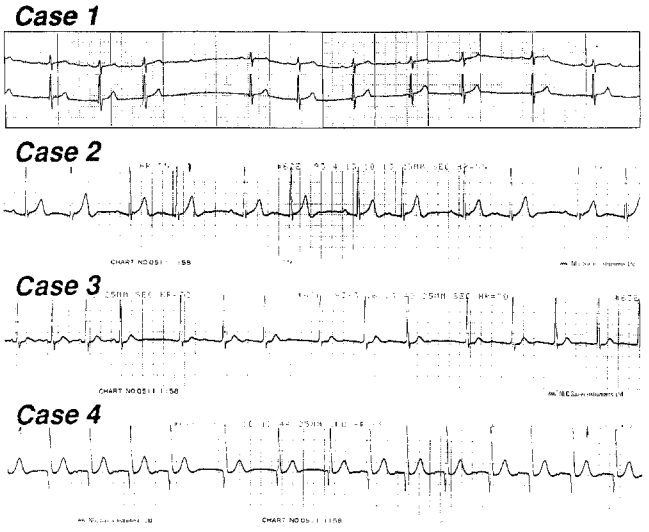

Fig. 1 Representative abnormal ECGs obtained in each patient described in Table 1. These changes were seen frequently for a few days and disappeared several days after granisetron administration

P-Q intervals were elongated in cases 1, 2, and 4, indicating the presence of AV block (Fig. 1). In cases 1 and 4, a progressive increase in AV conduction time was observed with each beat suggesting an AV nodal Wenckebach arrhythmia, although periodical complete block of conduction through the AV node was observed only in case 1 (Fig. 1). These changes were seen for a few days, with a return to a normal sinus rhythm being noted after several days.

Suppressed heart rate

All of the patients receiving granisetron exhibited a tendency to bradycardia, although the suppression of heart rates was not statistically significant because of the dynamic daily change in heart rate occurring in each patient. A patient with OS (case 1) showed persistent bradycardia which is designated as a continuously suppressed pulse rate lasting for 2 days, including episodes of less than 50 beats per minute persisting for at least 5 min (Table 1). The bradycardia was observed 30 min after the administration of granisetron and before the administration of chemotherapeutic drugs. This persistent bradycardia was observed in three courses of chemotherapy with high-dose MTX and VCR. At all times the persistent bradycardia was accompanied by the ECG changes described above. Furthermore, the patient complained of chest pressure during one course of treatment 2 h after the administration of granisetron. Holter ECG monitoring of this patient revealed a tendency to bradycardia, with normal sinus rhythm returning at night when he was not receiving chemotherapy.

Other adverse events

Headache was reported by one patient in whom no cardiac effect was seen. Diarrhea was seen in most patients. However, the relationship of this symptom in the lower digestive tract to granisetron is unclear because most of the chemotherapeutic agents used in the present study here can induce diarrhea.

Antiemetic efficacy

The antiemetic efficacy of granisetron was satisfactory, although a systemic evaluation was not performed. Especially, all four patients who had previously received other antiemetic agents expressed a preference for granisetron. Furthermore, in two of four patients who had previously experienced minor convulsions induced by cytotoxic chemotherapy the episodes were completely suppressed by the use of granisetron.

Discussion

In the present study, obvious arrhythmia on the ECG was observed in 4 of 12 cases. Cardiac changes did not seem to be correlated with any particular chemotherapeutic regimens. ECG changes were seen in OS, MFH, and rhabdomyosarcoma, indicating a lack of correlation between the cardiac reactions and the tumor type. These changes were seen for a few days, with a return to a normal sinus rhythm being noted after several days. This time course corresponds to the pharmacokinetics of granisetron [25]. Furthermore, the bradycardia had been observed 30 min after the administration of granisetron, before the injection of any chemotherapeutic drug, suggesting that the cardiac reactions are related to granisetron.

Upward et al. [25] found no important change in pulse rate, blood pressure or ECG in any healthy volunteer even at granisetron doses of up to 300 μg/kg. Their results seem to be inconsistent with the present findings. However, it has been pointed out that total-body-clearance values obtained for granisetron are lower and that the area under the plasma concentration-time curve is higher in cancer patients than in healthy volunteers [21]. Complications such as dehydration, electrolyte imbalance, and malnutrition can also occur in patients receiving chemotherapeutic regimens [12]. These factors may lead to differences in cardiac responses to granisetron in patients with malignant tumors versus healthy volunteers. Furthermore, drug interaction with concomitantly given antineoplastic agents may also influence the elimination of granisetron [1]. In our study, persistent bradycardia was observed only in the courses with high-dose MTX treatment, implicating high-dose MTX in the augmentation of the cardiac reaction to granisetron. On the

other hand, Elliott et al [7] have reported that the drug behaves as an unsurmountable antagonist at higher concentrations, suggesting a "pseudo-irreversible" antagonism due to slow dissociation of antagonist from the receptor. The present observation of cardiac effects only after several courses suggests that induction of the reaction may require the accumulation of granisetron at the effective sites with repeated use.

Suppressed heart rate, AV block with Wenckebach phenomenon, and ectopic escape rhythm were the alterations in the heart found in the present study. Most, if not all, of them are induced primarily by stimulation of vagal efferent activity. For example, an increase in parasympathetic activity prolongs the AV conduction time and induces bradycardia [24, 26]. A brief burst of vagal stimulation elicits an AV-nodal Wenckebach arrhythmia [27]. Increasing vagal activity results in further suppression of sinus activity and then secondary pacemakers (escape phenomenon) can assume automaticity, producing ectopic atrial, AV junctional, or idioventricular rhythms [10]. The response of AV conduction to vagal stimulation is essentially independent of the diverse sympathetic nervous system [27]. The cardiac changes described herein thus suggest stimulated activity of the vagal efferent nerve in patients receiving granisetron. This hypothesis that vagus dominant features are induced by the administration of granisetron may be supported by the findings that diarrhea and constipation, the major side effects of granisetron, are induced by disorders of the normal motor and secretory functions of the colon, which is under the control of the vagus nerve [18].

The vagal afferent nerve plays an important role in the generation of nausea and vomiting [2, 3, 11, 19]. Granisetron inhibits serotonin (5-hydroxytryptamine, 5-HT)-induced depolarization and reduction of the C spike in the rabbit vagus nerve [7]. It has been well recognized that suppressed signals through the vagal afferent fiber are closely associated with the antiemetic action of granisetron [2,21], although it remains controversial as to whether the sites of the drug's antagonistic action against 5-HT_3 receptors are located in the peripheral terminal of the nerve in the gut [19] or in the central terminal in the brain [15,20]. It is therefore suggested that granisetron may suppress the activity of the vagal afferent nerve, after which a feedback mechanism may stimulate the activity of the vagal efferent nerve, leading to the induction of alterations in the heart, since vagal efferent nerve activity contributing to the response of the heart is reflexly regulated by the vagal afferent nerve [13].

To the best of our knowledge, this is the first report describing a cardiac response to granisetron in a clinical setting. From the antiemetic point of view, our results confirm the excellent efficacy reported previously [4,14,16]. Chest pressure was reported only once, and most cardiac responses were silent and reversible. Thus, the present results, do not suggest that granisetron be restricted in patients treated with chemotherapy inducing nausea and vomiting. Our series was accidentally male-dominant. The relationship between cardiac reaction and sex is unclear. Fake et al. [8] reported a direct action of granisetron on the isolated heart. To elucidate in detail the actual mechanisms by which the heart responds to granisetron, further examination and careful observation are necessary to guide the administration of this useful and potent antiemetic drug, especially in patients receiving chemotherapy consisting of repeated multiple courses.

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