Cancer Chemother Pharmacol (1996) 37: 502–504

SHORT COMMUNICATION

Ismo T. Jantunen · Vesa V. Kataja · Timo T. Muhonen
Tapani Parviainen

Effects of granisetron with doxorubicin or epirubicin on ECG intervals

Received: 31 May 1995 / Accepted: 5 September 1995

Abstract Commercially available serotonin-type 3 (5-HT_3) receptor antagonists (ondansetron, granisetron, and tropisetron) have shown no clinically significant adverse effects on the cardiovascular system. In the dose-ranging evaluation of dolasetron, computer-generated ECGs revealed clinically asymptomatic prolongations of ECG intervals. We performed a clinical trial in which the possible changes in ECG intervals following a single 3-mg i.v. injection of granisetron and an injection of either doxorubicin or epirubicin were registered using computerized ECG analysis in cancer patients. A total of 30 patients who were designated to receive 3 mg granisetron i.v. for the prophylaxis of emesis induced by doxorubicin or epirubicin were entered into the study. Computer-generated ECG tracings were obtained before treatment, following the injection of 3 mg granisetron, and immediately after doxorubicin or epirubicin injection. The mean PR interval duration increased from 160 to 166 ms after granisetron infusion (P = 0.02). Doxorubicin and epirubicin did not potentiate this change. There was no statistically significant change in cardiac rhythm, QRS duration, or QTc intervals. The observed minor changes in the PR time following i.v. injection of granisetron do not seem to be of clinical relevance.

Key words Doxorubicin · ECG · Epirubicin · Granisetron

I. T. Jantunen (✉)
Department of Radiotherapy and Oncology, Central Hospital of Central Finland, Keskussairaalantie 19, FIN-40620 Jyväskylä, Finland

V. V. Kataja
Department of Radiotherapy and Oncology, Kuopio University Hospital, Kuopio, Finland

T. T. Muhonen
Department of Radiotherapy and Oncology, Helsinki University Central Hospital, Helsinki, Finland

T. Parviainen
Department of Clinical Physiology, Central Hospital of Central Finland, Jyväskylä, Finland

Introduction

The discovery of selective serotonin-type 3 (5-HT_3) receptor antagonists for the prophylaxis of chemotherapy-induced emesis has been a major advance in medical oncology. The antiemetic efficacy of 5-HT_3 receptor antagonists has been demonstrated in several clinical trials. A combination of dexamethasone and 5-HT_3 receptor antagonist prevents acute vomiting in 60% of patients receiving high-dose (>100 mg/m^2) cisplatin chemotherapy [3] and in 90% of patients receiving moderately emetogenic chemotherapy [7]. In addition to their high efficacy, a great advantage of these modern antiemetics has been their ease of administration and favorable safety profile. The commercially available 5-HT_3 receptor antagonists ondansetron, granisetron, and tropisetron have shown no clinically significant effect on the cardiovascular or central nervous system, including extrapyramidal effects [2]. Mild headache is the most frequently reported adverse event associated with the serotonin antagonists [2].

Acute cardiac arrhythmias have been observed in association with the administration of Taxol [8], doxorubicin [11], cisplatin [5], and 5-fluorouracil [6]. The exact mechanisms of these chemotherapy-induced arrhythmias are unknown. Since no cardiac adverse event has been causally associated with the registered serotonin antagonists that have been in clinical use for several years, it is unlikely that these modern antiemetics potentiate the possibility of chemotherapy-induced arrhythmias. The pharmaceutical industry has developed several new highly selective 5-HT_3 receptor antagonists. Batanopride is a substituted benzamide that acts as a highly selective 5-HT_3 receptor antagonist [1]. Clinical investigations of batanopride for the treatment of chemotherapy-induced emesis have been discontinued because of symptomatic hypotension and prolongation of the corrected QT interval (QTc), PR interval, and QRS complex on the ECG at clinically effective doses [1, 9]. Dolasetron mesylate (MDL 73,147EF) is a specific 5-HT_3 receptor antagonist that possesses class I antiarrhythmic activity [4]. A single i.v. infusion of dolasetron is

effective in the prophylaxis of emesis induced by high-dose cisplatin chemotherapy [4]. In the dose-ranging evaluation of dolasetron, computer-generated ECGs were obtained before and at 1–2 h after the dolasetron mesylate infusion. In a comparison of pretreatment ECGs with tracings taken at 1–2 h after dolasetron mesylate administration, dose-related prolongation of computer-generated PR, QRS, and QTc intervals have been observed [4]. Most of these clinically asymptomatic prolongations were statistically significant with a mean increment of 10–15 ms. The authors emphasize that such small prolongations are not apparent on visual inspection of ECGs and become evident only on computer-generated ECG tracings that electronically compute the intervals. The authors also indicate that although 5-HT_3 antagonists now in use have not been shown to cause cardiovascular side effects in cancer patients, no prior trial has reported the results of computer-generated ECGs obtained before and at 1–2 h after infusion of the available 5-HT_3 antagonist antiemetics.

We performed a clinical trial in which the possible changes in ECG intervals after a single 3-mg i.v. injection of granisetron and then after an injection of either doxorubicin or epirubicin were registered using computerized ECG analysis in cancer patients.

Patients and methods

The patients were eligible for the study if they were at least 18 years of age and designated to receive granisetron in the prophylaxis of emesis induced by doxorubicin- or epirubicin-containing chemotherapy. Patients who had received previous chemotherapy as well as chemotherapy-naive patients were included in the study. Exclusion criteria were: an unstable heart rhythm, clinical signs of congestive heart failure or active angina, and the use of 5-HT_3 receptor antagonists within 3 days of the start of chemotherapy. Verbal informed consent was obtained from all patients.

The 12-lead ECG was recorded on a Siemens Sicard 440 European standard analyzing 3/6 channel ECG recorder. The PR interval, ORS duration and QT/QTc time were analyzed by the analyzing program included. Following the pretreatment ECG tracing, 3 mg granisetron was given as a 5-min, constant-rate i.v. infusion. The second ECG tracing was obtained immediately after granisetron infusion followed by doxorubicin or epirubicin injection. The postchemotherapy ECG tracings were obtained at 5–10 min after the granisetron infusion. All patients were observed for at least 2 h.

The statistical calculations were performed using the Statview 4.02 and Statistica package for the Macintosh. The normality of distributions was first verified with the use of probit analysis. The descriptive statistics, including means and medians, were calculated with standard methods. The paired *t*-test was used for calculating the statistical significance of mean differences at different time points. *P* values below 0.05 were considered statistically significant.

Results

From October 1994 to January 1995, 30 patients were entered into the study. The characteristics and chemotherapy regimens of the patients are shown in Table 1. The observed changes in ECG intervals are shown in Table 2. The mean PR interval duration increased from 160 to 166 ms after granisetron infusion ($P = 0.02$). Doxorubicin and epirubicin did not potentiate this change, which was clinically asymptomatic in all of the patients. There was no statistically significant change in cardiac rhythm, QRS duration, or QTc intervals. Clinically significant cardiac effects did not occur.

Table 1 Patients' characteristics and chemotherapy given

Number of patients	30
M/F	16/14
Mean age (years)	55.2
Age range	25–80
Type of malignancy (number of patients)	
Breast	11
Lymphoma	4
Sarcoma	4
Lung	4
Prostata	4
Gastrointestinal	1
Melanoma	1
Adenocarcinoma, metastatic	1
Median dose of doxorubicin	40 mg/m^2
Dose range	20–100 mg/m^2
Median dose of epirubicin	40 mg/m^2
Dose range	10–50 mg/m^2

Table 2 Effects of granisetron and doxorubicin/epirubicin on the heart rate and on ECG intervals (*bpm* Beats per minute)

Heart rate and ECG intervals	Pretreatment	After granisetron injection	After doxorubicin/ epirubicin injection
Mean heart rate	82 bpm	82 bpm	80 bpm
Median heart rate	81 bpm	81 bpm	77 bpm
Range	55–110 bpm	55–109 bpm	61–103 bpm
Mean PR	160 ms	166 ms*	164 ms
Median PR	159 ms	167 ms	169 ms
Range	100–210 ms	124–218 ms	100–226 ms
Mean QRS	92 ms	92 ms	93 ms
Median QRS	92 ms	95 ms	94 ms
Range	78–108 ms	74–114 ms	78–110 ms
Mean QTc	425 ms	426 ms	427 ms
Median QTc	421 ms	426 ms	428 ms
Range	380–458 ms	380–478 ms	394–471 ms

* $P = 0.02$

Discussion

The normal duration of the PR interval in the adult ranges from 120 to 200 ms. Prolonged atrioventricular (AV) conduction (first-degree AV block) is characterized by a PR interval longer than 200 ms. Since the PR interval is determined by atrial, AV nodal, and Purkinje activation, any delay in one or more of these structures can contribute to a prolonged PR interval. In the presence of a normal QRS complex, a PR interval of over 240 ms is almost invariably due to a delay in the AV node.

The AV node is supplied by the parasympathetic and sympathetic nervous systems and is sensitive to variations in autonomic tone, It is highly sensitive to a variety of

external and internal stimuli, including certain infectious diseases, acute myocardial processes, biochemical derangements, and a number of drugs.

In eight healthy volunteers examined in a previous study, the mean PR interval duration increased from 170 to 174 ms after administration of the highest dose of granisetron (300 μg/kg); however, the mean PR interval duration increased from 169 to 176 ms after placebo infusion as well [10]. The present findings show that a single i.v. 3-mg injection of granisetron results in an asymptomatic increase in the PR duration, which nonetheless remains within normal limits. Whether this is a true effect of graniseteron on the AV node or on the conductance of the myocardial cell membranes remains to be established. The possibility of a physiological phenomenon in a stressful situation cannot be excluded either. However, the observed electrophysiological alteration is simply a numerical finding and has no clinical significance.

The results of this study further emphasize the remarkable safety profile of granisetron, which also holds true for the other commercially available 5-HT_3 receptor antagonists. Despite theoretical concern about the potential of 5-HT_3 antagonists to cause cardiac arrhythmias, these agents have not shown any clinically relevant arrhythmogenic effects.

References

1. Fleming GF, Vokes EE, McEvilly JM, et al. (1991) Double-blind, randomized crossover study of metoclopramide and batanopride for prevention of cisplatin induced emesis. Cancer Chemother Pharmacol 28: 226–227
2. Gralla RJ (1993) Adverse effects of treatment. In: DeVita VT, Hellman S, Rosenberg SA (eds) Cancer: principles and practice of oncology, 4th edn. Lippincott, Philadelphia pp 2341–2343
3. Hesketh PJ, Harvey WH, Harker WG, et al (1994) A randomized, double-blind comparison of intravenous ondansetron alone and in combination with intravenous dexamethasone in the prevention of high-dose cisplatin-induced emesis. J Clin Oncol 12: 596–600
4. Kris MG, Grunberg SM, Gralla RJ, et al (1994) Dose-ranging evaluation of serotonin antagonist dolasetron mesylate in patients receiving high-dose cisplatin. J Clin Oncol 12: 1045–1049
5. Menard O, Martinet Y, Lamy P (1991) Cisplatin-induced atrial fibrillation. J Clin Oncol 9: 192–193
6. Rezkalla S, Kloner RA, Ensley J, et al (1989) Continuous ambulatory ECG monitoring during fluorouracil therapy: a prospective study. J Clin Oncol 7: 509–514
7. Roila F, De Angelis V, Del Favero A, et al (1994) Antiemetic efficacy and tolerability of dexamethasone (DEX) vs granisetron (GRAN) vs GRAN+DEX in patients (Pts) submitted to moderately emetogenic antineoplastic agents (MEAA): a double-blind randomized multicentre study (abstract 994). Proceedings, 19th congress of the European Society for Medical Oncology, Lisbon, p 994
8. Rowinsky EK, McGuire WP, Guarniere T, et al (1991) Cardiac disturbances during the administration of Taxol. J Clin Oncol 9: 1704–1712
9. Smaldone L, Murphy W, Dombernowsky P, et al (1990) Antiemetic activity of batanopride (BMY-25801) in patients receiving cisplatin: a randomized double-blind parallel comparison of two doses (abstract). Proceedings, 17th congress of the European Society for Medical Oncology, Copenhagen, p 109
10. Upward JW, Arnold BD, Link C, et al (1990) The clinical pharmacology of granisetron (BRL 43694), a novel specific 5-HT_3 antagonist. Eur J Cancer 26 [Suppl 1]: 12–15
11. Wortman JE, Lucas VS, Schuster E, et al (1979) Sudden death during doxorubicin administration. Cancer 44: 1588–1591