

Effect of Antiemetic Agents on Hiccups during Chemotherapy in Patients with Lung Cancer

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Abstract

Hiccups commonly occur in patients undergoing chemotherapy for lung cancer and may diminish their motivation for treatment. Therefore, it is important to characterize the hiccups and their risk factors. We examined the medical records of 120 patients with lung cancer during their initial chemotherapy and extracted data on the patients' profiles and the onset, duration, and severity of their hiccup episodes. We found the incidence of hiccups to be 19.2% among the patients. Hiccups appeared within 3 days of beginning the chemotherapy and disappeared within 4 days. Hiccups hindered sleep in two patients. The characteristics of the hiccups episodes in our study were not different from those of previous studies. We also investigated distinctive features of the patients who developed hiccups. The occurrence of hiccups was associated with gender, age, and the treatment with platinum agents. Antiemetic agents, dexamethasone and neurokinin-1 receptor antagonists, also showed significant effects on hiccup episodes. Although the dose-responsive effect of dexamethasone on hiccups was insignificant and the effects of two neurokinin-1 receptor antagonists, aprepitant and fosaprepitant, on hiccups appeared identical. From these results, we suggest that a high incidence of hiccups may be anticipated with a prophylactic use of antiemetic agents, dexamethasone and neurokinin-1 receptor antagonists.

Keywords

Hiccups, Dexamethasone, Neurokinin-1 Receptor Antagonist, Antiemetic Agents, Lung Cancer

1. Introduction

Hiccups are common physical phenomena noted by a specific "hic" sound that is

produced by involuntary contractions of respiratory muscles (including diaphragm and intercostal and anterior scalene muscles) followed by a sudden closure of the vocal cords [1] [2]. Spontaneous hiccups in healthy subjects are usually self-limited and short-lived. Thus, most cases do not require medical treatment. There are also various pathophysiological conditions that stimulate a hiccup reflex neural pathway to trigger bouts of hiccups [3].

Indeed, rare intractable hiccups may indicate the existence of serious underlying problems in patients. Some pharmacological agents are also known to be risk factors for hiccups [4]. In patients with lung cancer, hiccups can be associated with the anticancer drug cisplatin [5] as well as with the antiemetic agent dexamethasone [5] [6] and neurokinin-1 receptor antagonist [7]. Although hiccups will rarely put a patient's life at risk, they appear to negatively impact patient's daily activities and their motivation for chemotherapy. Therefore, understanding hiccups is important to identify the associated factors during cancer treatment. Few studies of antiemetics agents have been conducted on the associations among risk factors. Here we examined the characteristics of hiccups and associated risk factors during the first chemotherapy cycle in patients with lung cancer.

2. Subjects and Methods

2.1. Study Design

This is a single-center retrospective cohort study investigating the characteristics and associated risk factors of hiccups during the first chemotherapy cycle in patients with lung cancer.

2.2. Patients

We retrospectively examined the medical records of all inpatients who received their first chemotherapy cycle for lung cancer in the National Hospital Organization East Saitama Hospital from October 2011 to March 2013. Participants were followed 3 weeks after the beginning of chemotherapy. Exclusion criteria were as follows: those who tolerated chemotherapy poorly and those already with hiccups episodes before the beginning of their chemotherapy. All patients were treated with cisplatin, carboplatin, or with non-platinum-based antineoplastic drugs (non-Pt). Cisplatin was injected at doses of 70 to 90 mg/m² on day 1. Carboplatin was injected at doses of 5 - 6 AUC on day 1. In addition, all patients received antiemetics including dexamethasone, 5-hydroxytryptamine receptor antagonist (5-HT₃RA), and/or neurokinin-1 receptor antagonist (NK1RA) before and during chemotherapy to prevent or minimize chemotherapy-related emesis. One of two doses of dexamethasone was administered to each patient. In dexamethasone 6.6 mg group (DEX 6.6 mg), 6.6 mg of dexamethasone was injected on day 1 while in dexamethasone 16.5 mg group (DEX 16.5 mg), 16.5 mg of dexamethasone was injected on day 1 and 6.6 mg on day 2 and 3. Regarding 5HT₃ RA administration, granisetron was injected at a dose of 3 mg on day 1 or

palonosetron was injected at a dose of 0.75 mg on day 1. For NK1RA, aprepitant was orally administered at a dose of 125 mg on day 1 and 80 mg on day 2 and 3 or fosaprepitant was injected at a dose of 150 mg on day 1. Neuroleptic agents were also used according to clinical needs.

2.3. Clinical Assessment

In this cohort, we tried to answer two questions related to hiccups during anti-cancer treatment: 1) what were the characteristics of the hiccups and 2) what factors influenced the occurrence of hiccups. The severity of hiccups was determined using a grading scale created by the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0), consisting of three grades: Grade 1 includes only the hiccups and does not require treatment, Grade 2 includes hiccups that require treatment, and Grade 3 includes hiccups that significantly hinder sleep and daily life. Information on patient clinical characteristics, laboratory data, and medication were collected from the medical records. Data on the occurrence, frequency, duration, and severity of hiccups were all used in the analysis. Medical records of hiccups used in the present study were carefully monitored on the bed side.

2.4. Statistical Analysis

Data are expressed as mean \pm standard deviation. Categorical variables are expressed as numbers, frequencies, and percentages. Comparisons between the group with hiccups and the group without hiccups were performed using the Mann-Whitney U-test, chi-square test or the fisher's exact test, as appropriate. To identify risk factors for hiccups. A *P* value of <0.05 was considered significant. All statistical analyses were performed using JMP® Pro 13.1.0 (SAS Institute Inc., Cary, NC, USA).

2.5. Ethics Regulation

This retrospective study using medical records was undertaken with the approval of the Ethics Committee of the hospital. We complied with the Declaration of Helsinki and the Ethical Guidelines for Epidemiological Research.

3. Results

3.1. Characteristics of Hiccups

Of a total of 120 Japanese patients admitted for receiving their first chemotherapy cycle for lung cancer, none was excluded based on the exclusion criteria. Hiccups were observed in 23 of 120 patients undergoing the initial chemotherapy cycle for lung cancer. All patients developed hiccups within 3 days of beginning the chemotherapy, and the episodes lasted for a maximum of 4 days (**Figure 1**). More precisely, the first bout of hiccups occurred on the first day of chemotherapy in five patients, on the second day in seventeen patients, and on the third day in one patient (**Figure 1(a)**). Hiccups lasted for 1 day in five

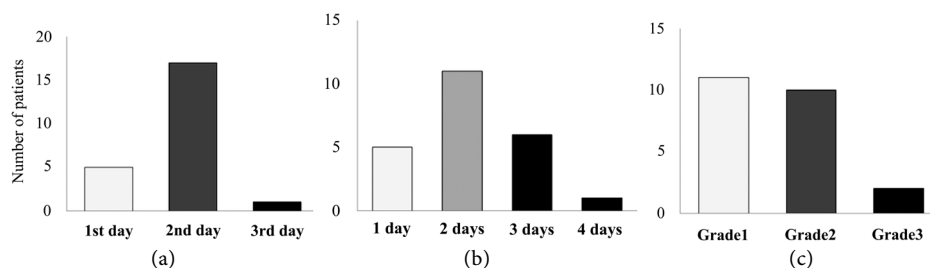


Figure 1. Onset (a); duration (b); and severity (c) of hiccups in patients with lung cancer undergoing the first chemotherapy cycle.

patients, 2 days in eleven patients, 3 days in six patients, and 4 days in one patient (**Figure 1(b)**). The mean duration was 3 days.

Regarding the severity of hiccups, eleven patients had grade level 1 hiccups, ten patients grade level 2, and two patients grade level 3 (**Figure 1(c)**). The hiccups hindered sleep in two (1.7%) patients. One of the two patients was treated with a cisplatin based chemotherapy and 6.6 mg of dexamethasone, palonosetron, and aprepitant as prophylactic antiemetics. The other patient was cared with the carboplatin based chemotherapy and DEX 16.5 mg, granisetron, and fosaprepitant as an antiemetics agents. Eight patients needed to be treated for the hiccups, and baclofen was found to be curative.

3.2. Comparison of Background Patient Characteristics

The baseline characteristics of the patients who experienced hiccups were similar to those of the patients without hiccups, except for gender, age and use of anti-cancer agents and antiemetics agents (**Table 1**). None of the 23 female patients developed hiccups ($P = 0.006$). Hiccups developed in relatively younger subjects ($P = 0.045$). More patients in the hiccups group used platinum antitumor agent ($P = 0.014$), dexamethasone ($P = 0.022$), and NK1RA ($P = 0.048$) than those in the non-hiccups group. Patients using 5HT3 RA as an antiemetic did not increase in the incidence of hiccups ($P = 0.154$; **Table 1**).

3.3. The Incidence of Hiccups and Antiemetic Agents

The incidence of hiccups increased in patients using dexamethasone as an antiemetic. For details, the incidence of hiccups in patients treated with 6.6 mg of dexamethasone as well as the cisplatin based chemotherapy was 38.9% and that in patients using carboplatin was 20.0%, whereas the incidence of hiccups in patients using non platinum based chemotherapy was 12.5% (**Table 2**). However, we found no differences in the incidence of hiccups with the uses of 6.6 mg of dexamethasone under different chemotherapy protocols. In patients using the carboplatin based chemotherapy, two doses of dexamethasone were administered. Using the carboplatin, the incidence of hiccups in patients taking 6.6 mg of dexamethasone was again 20.0% and that with a total dose of 29.7 mg dexamethasone was 50.0%. However, there was no significant difference in the incidence of hiccups between two doses of dexamethasone.

Table 1. Correlation of hiccups with patients' characteristics.

| Parameter | No. of Patients | Patients with Hiccups | | |
|--------------------------|-----------------|-----------------------|-------|----------|
| | | No. of Patients | % | <i>P</i> |
| Total | 120 | 23 | 19.2 | |
| Gender | | | | 0.006 |
| Male | 97 | 23 | 23.7 | |
| Female | 23 | 0 | 0.0 | |
| Age | 71.6 ± 8.2 | 68.5 ± 6.5 | | 0.045 |
| Staging | | | | 0.520 |
| 1 | 4 | 1 | 25.0 | |
| 2 | 8 | 0 | 0.0 | |
| 3 | 30 | 7 | 23.3 | |
| 4 | 78 | 15 | 19.2 | |
| Performance Status | | | | 0.093 |
| 1 | 106 | 18 | 17.0 | |
| 2 | 8 | 2 | 25.0 | |
| 3 | 5 | 2 | 40.0 | |
| 4 | 1 | 1 | 100.0 | |
| Lung surgery | 65 | 9 | 39.1 | 0.108 |
| Brain metastasis | 17 | 3 | 13.0 | 0.864 |
| Diaphragm metastasis | 28 | 6 | 26.1 | 0.728 |
| Medication history | | | | |
| Platinum antitumor agent | 77 | 20 | 26.3 | 0.014 |
| Antiemetic agent | | | | |
| DEX | 101 | 23 | 22.8 | 0.022 |
| 5HT3RA | 107 | 23 | 21.5 | 0.154 |
| NK1RA | 87 | 21 | 24.1 | 0.048 |

DEX, dexamethasone; 5HT3RA, 5-hydroxytryptamine receptor antagonists; NK1RA, Neurokinin 1 receptor antagonists.

In patients using NK1RA as an antiemetic, the incidence of hiccups was increased as shown in **Table 1**. In the present study, two types of NK1RAs, aprepitant and fosaprepitant, were used. For details, aprepitant was administered to 30 patients and 9 of them (30%) were with hiccups, while fosaprepitant was given to 57 patients and 12 (21.1%) had hiccups. Regarding the effect of the combination of NK1RA and platinum-based regimen medications on the incidence of hiccups, we found no differences between the group of patients taking aprepitant and the group of patients being treated with fosaprepitant, irrespective of whether they received the cisplatin based chemotherapy or carboplatin based one (**Table 3**).

Table 2. The incidence of hiccups and dose effects of dexamethasone under different types of chemotherapy.

| | Patients with Hiccups | | Patients without Hiccups | | Within the group | <i>P</i> | | |
|---------------------------------|-----------------------|------|--------------------------|-------|------------------|----------|-------|-------|
| | No. | % | No. | % | | vs. a | vs. b | vs. c |
| Non platinum based chemotherapy | | | | | NE | | | |
| None | 0 | 0.0 | 19 | 100.0 | | | | |
| DEX 6.6 mg | 3 | 12.5 | 21 | 87.5 | | 0.164 | | |
| DEX 16.5 mg | 0 | 0.0 | 0 | 0.0 | | | | |
| CBDCA based chemotherapy | | | | | NE | | | |
| None | 0 | 0.0 | 0 | 0.0 | | | | |
| DEX 6.6 mg | 11 | 20.0 | 44 | 80.0 | | 0.029 | 0.323 | |
| DEX 16.5 mg | 2 | 50.0 | 2 | 50.0 | 0.208 | 0.024 | | |
| CDDP based chemotherapy | | | | | NE | | | |
| None | 0 | 0.0 | 0 | 0.0 | | | | |
| DEX 6.6 mg | 7 | 38.9 | 11 | 61.1 | | 0.003 | 0.053 | 0.970 |
| DEX 16.5 mg | 0 | 0.0 | 0 | 0.0 | | | | |

CDDP, cisplatin; DEX, dexamethasone; NE, not examined; a, None in the Non platinum based chemotherapy; b, DEX 6.6 mg in the Non platinum based chemotherapy; c, DEX 6.6 mg in the CBDCA based chemotherapy.

Table 3. Comparison of the incidence of hiccups between aprepitant and fosaprepitant under cisplatin or carboplatin based chemotherapy.

| | Patients with Hiccups (n = 20) | | Patients without Hiccups (n = 62) | | Within the group | <i>P</i> | Between the groups |
|--------------------------|--------------------------------|------|-----------------------------------|------|------------------|----------|--------------------|
| | No. | % | No. | % | | | |
| CBDCA based chemotherapy | | | | | 0.760 | | |
| Aprepitant | 5 | 22.7 | 17 | 77.3 | | | |
| Fosaprepitant | 8 | 19.5 | 33 | 80.5 | | | |
| CDDP based chemotherapy | | | | | 0.141 | | |
| Aprepitant | 4 | 57.1 | 3 | 42.9 | | | 0.108 |
| Fosaprepitant | 3 | 25.0 | 9 | 75.0 | | | 0.797 |

CBDCA, carboplatin; CDDP, cisplatin.

4. Discussion

In the present study, hiccups developed in 23 patients with lung cancer during their first cycle of chemotherapy. Hiccups appeared within 3 days of beginning the chemotherapy, and the mean duration of hiccups was 3 days. The severity of hiccups varied from grade 1 to grade 3. Because female patients did not develop hiccups, there was definitely a male dominance. Comparison analyses between the group of patients with hiccups and the group of patients without them re-

vealed that gender, age, platinum antitumor agents, dexamethasone, and NK1RA are associated with the increased incidence of hiccups in patients with lung cancer undergoing chemotherapy.

The characteristics of the hiccups episodes in our study were not different from those of previous studies. Hiccups occurred in 23 (19.2%) out of 120 patients, which is at an intermediate point in the reported 5% - 40% [5] [8] [9]. Therefore, hiccups are not rare during lung cancer chemotherapy. The time courses and severities of the hiccup episodes in our patients were also similar to those reported in previous studies [5] [10] [11]. The hiccups experienced by our patients were transient; they appeared within 3 days and disappeared within 4 days from the onset. Two patients had sleep disturbance caused by the hiccups, and eight patients needed treatment with baclofen. Baclofen was effective for the hiccups in our patients as previously reported [12]. With respect to the gender differences observed in our study, the general consensus is that male patients are more prone to the development of hiccups during this type of chemotherapy [4] [10]. However, no gender predispositions to hiccups have been reported in other clinical settings such as in patients with brain tumors or mediastinal disorders [1] [13]. We also recognized an importance in age. Hosoya *et al.* reported that the average age of patients with hiccups were 57.7 and is significantly older than that of patients without hiccups which was 53.6 [4]. The average age of patients with hiccups in the present study was 68.5 which was significantly younger than that of patients without hiccups. Taken together, there may be a certain period of age which are vulnerable in developing hiccups under treatment for lung cancer.

Hiccups observed during chemotherapy are considered medication-related symptoms. In the present study, we found an increased incidence of hiccups in patients on the platinum antitumor agents and on antiemetics agents including dexamethasone and NK1RA. Hiccups have been shown to be one of the adverse effects of platinum antitumor agents [4] [5]. Platinum antitumor agents are used against many types of cancers. Adverse effects of platinum agents include not only nausea and vomiting but also hiccups.

An antiemetic medication is recommended before the infusion of platinum antitumor agents [14] [15]. The patients in the present study were treated with dexamethasone, NK1RA, or 5HT3RA. However, antiemetics agents of chemotherapy can trigger hiccups, and dexamethasone and NK1RA has been associated with development of hiccups [5] [7]. Indeed, the present study confirmed that the use of dexamethasone play some role in the development of hiccups. The incidence of the hiccup with the dexamethasone administration in the present study was similar to those reported in a previous study [9]. We failed to observe a dose-dependent effect on the incidence of hiccups.

The use of NK1RA may also have played a role in the development of hiccups because we observed an increased use of the agent in the group of patients with hiccups in the present study. Studies have shown the incidence of hiccups varied

from 19% to 33% in patients who were treated with NK1RA [16]. NK1RA is reported to inhibit the activity of cytochrome P-450 3A4 (CYP3A4), a dexamethasone-metabolizing enzyme [17]. In consequence, it is possible that the inactivated CYP3A4 led to elevated dexamethasone levels in the blood in our patients. In fact, the combination of dexamethasone with NK1RA has been shown to increase the circulating dexamethasone levels in blood [17]. Although, our results cannot rule out the possibility that NK1RA alone may be a risk for triggering hiccups. The NK1RA used in this study included aprepitant or fosaprepitant, but the effects of two agents were not different on the incidence of hiccups. Fosaprepitant is an intravenous formulation of aprepitant that could convert to aprepitant in 30 minutes after the administration [18], and an intravenous dose of 115 mg of fosaprepitant is bioequivalent to oral dose of 125 mg of aprepitant [19].

Our study was a small-scale, retrospective, single-center study including older Japanese patients; thus, the results could not be directly extended to larger and younger populations or to other ethnic groups. However, medical records used in the present study were carefully monitored on the bed side. Because, mild hiccups are only occasionally reported on a self-reporting system.

5. Conclusion

In conclusion, we found that gender, age, and uses of platinum antitumor agents, dexamethasone, and NK1RA were risk factors for hiccups in patients with lung cancer. On the incidence of hiccups, we never observed dose responsive effects of dexamethasone or different effects between aprepitants and fosaprepitant. Therefore, to avoid hiccups in patients with lung cancer, we suggest caution on the use of dexamethasone and NK1RA in male and some certain-aged patients with lung cancer during their chemotherapy.

Conflict of Interest

We declare that we have no conflict of interest.

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