Pharmacology & Pharmacy, 2018, 9, 331-343
http://www.scirp.org/journal/pp
ISSN Online: 2157-9431
ISSN Print: 2157-9423

Risk Factors for Cancer Chemotherapy-Induced Hiccups (CIH)

Ryuichiro Hosoya[1,2], Ippei Tanaka[2], Reiko Ishii-Nozawa[3], Takeshi Amino[4], Tomoyuki Kamata[4], Seiichi Hino[2], Hajime Kagaya[5], Yoshihiro Uesawa[1*]

[1]Department of Medical Molecular Informatics, Meiji Pharmaceutical University, Kiyose, Japan
[2]Department of Pharmacy, Japanese Red Cross Musashino Hospital, Musashino, Japan
[3]Department of Clinical Neuropharmacology, Meiji Pharmaceutical University, Kiyose, Japan
[4]Department of Neurology, Japanese Red Cross Musashino Hospital, Musashino, Japan
[5]Department of Clinical Pharmaceutics, Meiji Pharmaceutical University, Kiyose, Japan
Email: *uesawa@my-pharm.ac.jp

How to cite this paper: Hosoya, R., Tanaka, I., Ishii-Nozawa, R., Amino, T., Kamata, T., Hino, S., Kagaya, H. and Uesawa, Y. (2018) Risk Factors for Cancer Chemotherapy-Induced Hiccups (CIH). *Pharmacology & Pharmacy*, **9**, 331-343.
https://doi.org/10.4236/pp.2018.98026

Received: July 16, 2018
Accepted: August 19, 2018
Published: August 22, 2018

Abstract

Background: Hiccups are common somatic side effects of medication. Our previous analysis of the clinical risk factors for hiccups identified chemotherapy as a factor related to hiccup risk. Therefore, in the present study, we investigated the risk factors for hiccups associated with chemotherapy. **Methods:** We included all patients who received cancer chemotherapy and were hospitalized at the Musashino Red Cross Hospital between April 2014 and December 2014. We investigated patient demographics, physical characteristics, and other clinical factors to identify the risk factors for chemotherapy-induced hiccups (CIH). We conducted univariate and multivariable analysis to compare the CIH group and the non-CIH and determined risk factors of CIH. **Results:** Hiccups were identified in 48 of 292 patients with an incidence rate of 16.4%. Univariate analysis revealed that the male gender, pain, and nausea and vomiting were related to CIH. It also showed that cisplatin, pemetrexed, gemcitabine, etoposide, dexamethasone, and metoclopramide were related to CIH.A correlation which was found with doses of cisplatin, pemetrexed, gemcitabine, and etoposide. Multivariable analysis identified male gender (OR, 72.69; 95% CI, 6.95 - 757.64), nausea and vomiting (OR, 52.01; 95% CI, 3.93 - 447.13), dexamethasone (OR, 4.55; 95% CI, 1.12 - 16.91), cisplatin (OR, 3.84; 95% CI, 1.52 - 9.70), and etoposide (OR, 3.72; 95% CI, 1.14 - 12.11) as independent risk factors for hiccups. **Conclusions:** The present study is the first one to report risk factors for the development of CIH. Our results suggest that male gender, having nausea, and the drugs dexamethasone, cisplatin, and etoposide are important risk factors for CIH. These results may assist in elucidation of the underlying mechanisms and guide therapy to reduce hiccup risk.

Keywords

Hiccups, Chemotherapy, Adverse Effects, Cancer, Risk Factors

1. Introduction

Most people experience hiccups occasionally. Hiccups are caused mainly by diaphragmatic myoclonus, a brief involuntary twitching of the diaphragmatic muscles, along with coordinated contraction of the glottic closure group of muscles [1]. It is reported that the glossopharyngeal nerve (ninth cranial nerve), vagus nerve (tenth cranial nerve), the nuclei of the solitary tract, the nucleus ambiguus, and the phrenic nerve are all involved in the afferent and efferent pathways of the hiccup reflex arc [2] [3] [4].

Although it is rare for hiccups to be life-threatening, they often lead to a decrease in quality of life. Wilcock A and Twycross reported that persistent hiccups can disturb verbal communication, sleep, eating, and drinking, and in severe cases can result in weight loss, exhaustion, anxiety, and depression [5]. Being able to control these symptoms is particularly important clinically, because treatment may be disturbed when hiccups occur as a side effect. However, the exact mechanisms behind the central link of the hiccup reflex arc are not very clear. Hiccups are classified based on duration as transient, hiccup bouts (within 48 hours), persistent (less than one month more than 48 hours), or intractable (over one month) [6]. Epidemiologically, persistent or intractable hiccups show male dominance. Lee GW *et al.* reported that hiccups of non-central nervous system (CNS) origin are more common among males [7].

In our previous study, we investigated patient physical information and medication contributing to hiccups using the large Japanese Adverse Drug Event Report Database [8]. Our findings suggested that the male gender, tall stature, anti-cancer drug use, and dexamethasone use are risk factors for hiccups.

More recently, chemotherapy-induced hiccups have been reported, particularly during treatment with cisplatin [9] [10]. In addition, it was found that antiemetic drugs including steroid drugs when combined with anti-cancer drugs may increase the risk of hiccups. Lee GW *et al.* succeeded in decreasing the induction of hiccups by changing patient medication from the antiemetic drug dexamethasone to methylprednisolone in a patient who developed hiccups as a result of a dexamethasone-containing chemotherapy regime [11]. They concluded that dexamethasone-induced hiccups may be controlled via steroid rotation. We reported that dexamethasone is an important drug associated with the induction of hiccups in our previous study [8]. We were unable to rule out the induction of hiccups due to anti-cancer drugs, because they induced hiccups in the absence of dexamethasone per our data. Thus, the association between chemotherapy and hiccups is becoming clear. However, no study has systematically evaluated the association between chemotherapy drugs and hiccups based on

clinical data.

We retrospectively evaluated risk factors for chemotherapy-induced hiccups by using clinical data that included patient information, symptoms, medications, and regimen of chemotherapy.

2. Materials and Methods

2.1. Database

We selected patients hospitalized at Musashino Red Cross Hospital between April 2014 and December 2014. We included all patients who received cancer chemotherapy and underwent hospitalization. We removed duplicate data of patients readmitted during the investigation period. Data of patients with CIH were connected to data of all other patients who received chemotherapy using the ID number to construct a data table (Figure 1). This study was approved by the clinical study and ethics committee of Musashino Red Cross Hospital (Application number, 27005).

2.2. Extraction of Patient Information

We defined hiccups that occurred within one week after chemotherapy as chemotherapy-induced hiccups (CIH). We extracted information regarding occurrence of CIH by searching for instances mentioned in the electronic medical charts of Musashino Red Cross Hospital. We judged the onset of the CIH from the description of a physician, a nurse or other medical staff in the medical

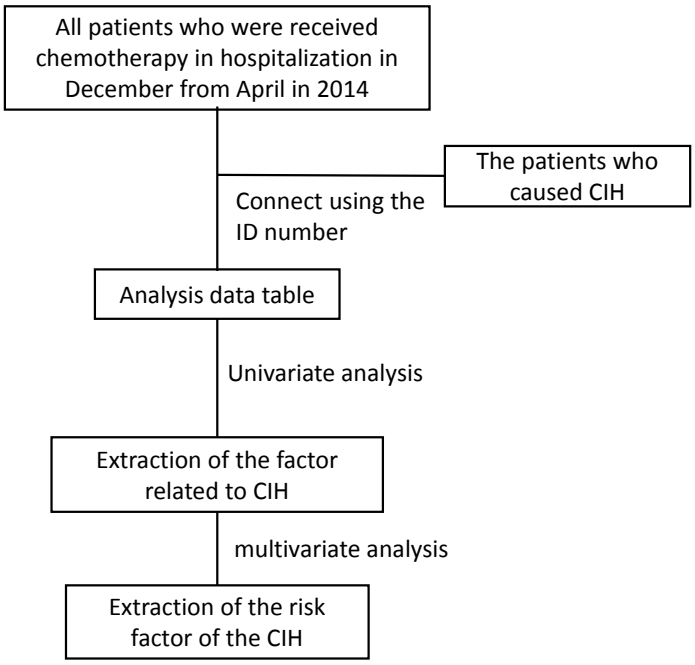

Figure 1. Data collection and analysis flowchart. We removed duplicate data from all patient data. The data of patients with hiccups after chemotherapy were connected to the data of all patients using ID numbers. We conducted univariate analysis and multivariate analysis to identify risk factors for chemotherapy-induced hiccups.

charts. We defined the patients who presented with hiccups within one week after chemotherapy as CIH group. The control group comprised the patients who underwent chemotherapy but did not experience hiccups as above.

2.3. Exclusion Criteria

The following patients were excluded.

1) Those who only were only given orally administered anti-cancer drugs.

2) Those who received chemotherapy in the outpatient department.

3) Those who only received hormonal cancer therapy.

4) Those who experienced hiccups only after more than seven days following chemotherapy.

2.4. Investigation of Patient Information

We retrospectively investigated patient physical information, name of disease, medical history, surgery, chemotherapy regimen, and medication using the electronic medical chart system. Further, we extracted data regarding tube insertion and symptoms such as nausea and pain. We also investigated CIH duration, frequency, triggers, and adverse effects. In the CIH group, we extracted patient information before and after CIH. In the control group, we extracted patient information at approximately the third day after chemotherapy was started.

2.5. Statistical Analyses

CIH and patient information

We compared data between the CIH and non-CIH patients regarding patient information, medication, and symptoms by using univariate analysis. We conducted univariate analysis to examine factors associated with CIH. For nominal variables, we compiled a cross-tabulation table based on the presence or absence of CIH and the presence or absence of patient information, and calculated *P* value and odds ratios (ORs) using the Fisher exact test. For continuous variables, we conducted t-tests and calculated the *P* value. Further, we conducted univariate analysis to evaluate the doses of drugs which were associated with significant differences between the CIH group and the non-CIH group.

2.6. Multivariable Analysis

We performed multivariable logistic regression analysis to evaluate the importance of each factor in CIH risk. The objective variable was CIH (YES/NO) and the explanatory variables were patient physical characteristics, clinical variables, symptoms, and medications that were found to have a significant effect in univariable analysis.

Means (±standard deviation) were calculated for all continuous variables. A *P*-value of <0.05 was considered significant. We estimated internal correlation using the pair wise method. When the square of Spearman's rank-order correlation coefficient [ρ^2] was greater than 0.9, we concluded that there was an internal

correlation. When there was no internal correlation, we treated these items as independent factors. All analyses were carried out with JMP®Pro13 (SAS Institute Inc., NC, USA).

3. Results

3.1. Patient Backgrounds and Tumor Types

In total, 292 patients were hospitalized at Musashino Red Cross Hospital and were treated using chemotherapy between April 2014 and December 2014. Hiccups were identified in 48 patients with an incidence rate of 16.4%.CIH occurred at an average of 1.7 ± 1.3 days after chemotherapy started. The results of univariate analysis comparing CIH and non-CIH are shown in Table 1. Males comprised >90% of the CIH group, and the gender difference was significant ($P < 0.0001$). In the non-CIH group, the mean patient age, height, weight, body mass index (BMI), and body surface area (BSA) were 64.1 ± 0.87 years, 160.23 ± 0.56 cm, 54.31 ± 0.76 kg, 21.05 ± 0.24, and 1.55 ± 0.01 respectively; in the CIH group, they were 61.9 ± 2.01 years, 165.91 ± 1.26 cm, 59.38 ± 1.70 kg, 21.55 ± 0.53, 1.65 ± 0.03, respectively. The data showed significant differences in height ($P < 0.0001$), weight ($P = 0.0068$), and BSA ($P = 0.0005$).

We conducted univariate analysis to evaluate the association of cancer type with presence or absence of CIH as the objective variable. The results of our analysis and the cancer types occurring in more than two patients in the CIH group are shown in Table 2. Cancer types significantly related to CIH were lung cancer ($P = 0.006$) and bladder cancer ($P = 0.019$). The incidence of CIH was 31.6% in patients receiving chemotherapy for lung cancer.

The adverse effects of CIH were insomnia (14.6%), pain (8.3%), and dysphasia (6.2%). In addition, fatigue, a feeling of pain, and shortness of breath were also associated with CIH. All analyses excluded patients with missing values.

3.2. CIH and Category of Anti-Cancer Drugs

We classified anti-cancer drugs based on their efficacy in the CIH and non-CIH

Table 1. Results of univariate analysis comparing patient data in the chemotherapy-induced hiccup group and the non-hiccup group.

	Total	Hiccups (n = 48)	Non-hiccups (n = 244)	*P*-value
Gender (M/W)#	157/135	46/2	111/133	<0.0001
Age*	292	61.9 ± 2.0	64.1 ± 0.87	0.2607
Height (cm)*	292	165.91 ± 1.26	160.225 ± 0.56	<0.0001
Weight (kg)*	292	59.38 ± 1.70	54.311 ± 0.76	0.0068
BMI*	292	21.55 ± 0.53	21.05 ± 0.24	0.3889
BSA	292	1.65 ± 0.026	1.55 ± 0.01	0.0005

Plus-minus values are means SD. M, Men; W, Women; BMI, Body Mass Index (Weight (kg)/Height $(m)^2$); BSA, Body Surface Area (0.20247 × height $(m)^{0.725}$ × weight $(kg)^{0.425}$); #: Hiccup and non-hiccup groups were compared using Fisher's exact test; *: Hiccup and non-hiccup groups were compared using a t-test.

Table 2. Results of univariate analysis comparing cancer type between the chemotherapy-induced hiccup group and the non-hiccup group.

Type of cancer	Total	Hiccup	non-Hiccups	*P*-value	Odds ratio	95% CI
Lung cancer	57	18	39	0.006	2.86	1.46 - 5.61
Gastric cancer	17	5	12	0.334	2.16	0.75 - 6.20
Malignant lymphoma	35	3	32	0.159	0.46	0.15 - 1.44
Acute lymphocytic leukemia	7	3	4	0.154	3.79	0.90 - 15.87
Neoplasm of esophageal	6	3	3	0.110	4.89	1.07 - 22.26
Bladder cancer	3	3	0	0.019	34.69	1.76 - 683.19

Hiccup and non-hiccup groups were compared using Fisher's exact test (n > 2 in Chemotherapy-Induced Hiccup patients).

groups. We conducted univariate analysis of the category of anti-cancer drugs with presence or absence of CIH the objective variable. The results are shown in Table 3. The categories of drugs significantly associated with increased CIH were platinum drugs ($P < 0.001$), antimetabolite agents ($P < 0.001$), and to poisomerase inhibitors ($P = 0.0086$). In contrast, patients using microtubule inhibitors ($P = 0.0007$) did not tend to experience hiccups.

Similarly, we conducted univariate analysis to identify the anti-cancer drug categories that were associated with significant differences. The results, shown in Table 4, identified cisplatin ($P < 0.0001$), pemetrexed ($P = 0.0112$), gemcitabine ($P = 0.0296$), and etoposide ($P = 0.0013$).

3.3. Association between CIH and Antiemetics

We conducted univariate analysis of the drug categories antiemetics and steroid drugs with presence or absence of CIH as the objective variable. The results of this univariate analysis are shown in Table 5. Further, the results of univariate analysis involving all antiemetic drugs and steroid drugs are shown in Table 5. Significant associations of CIH with antiemetics ($P < 0.0001$), and steroid drugs ($P < 0.0001$) were found. In the CIH group, all patients used steroid drugs, but only dexamethasone showed a significant association with CIH in the steroid group ($P < 0.0001$). In the group using antiemetics, 5-HT3 receptor antagonists ($P = 0.0241$) and metoclopramide ($P < 0.0001$) showed significant associations with CIH.

3.4. Association between Anti-Cancer Drug Dose and CIH

Table 6 shows the results of univariate analysis of dexamethasone and four other drugs to identify significant differences between the CIH and non-CIH groups. Cisplatin, pemetrexed, gemcitabine, and etoposide dose showed an association with CIH, while dexamethasone dose did not.

3.5. Association between CIH and Symptoms, Tube Insertion, and Medications

We conducted univariate analysis of patient symptoms, tube insertion, and

Table 3. Results of univariate analysis comparing anti-cancer drug categories between the chemotherapy-induced hiccup group and the non-hiccup group.

The category of anticancer medication	Total	Hiccups (n = 48)	Non-hiccups (n = 244)	*P*-value	Odda ratio	95% CI
Platinum drugs	130	40	90	<0.0001	8.56	3.84 - 19.09
Alkylating agents	41	5	36	0.5038	0.67	0.25 - 1.81
Antimetabolite agents	107	32	75	<0.0001	4.51	2.33 - 8.71
Antitumor antibiotic agents	46	8	38	0.83	1.08	0.47 - 2.50
Microtubule Inhibitors	81	4	77	0.0007	0.20	0.07 - 0.57
Topoisomerase inhibitors	37	12	25	0.0086	2.92	1.35 - 6.33
Molecular-target agents (Monoclonal antibodies)	32	3	29	0.3197	0.49	0.14 - 1.69
Molecular-target agents (Small molecules)	16	2	14	1	0.71	0.16 - 3.25

Hiccup and non-hiccups groups were compared using Fisher's exact test.

Table 4. Results of univariate analysis identifying anti-cancer drug categories associated with significant differences.

Anticancer medication	Total	Hiccups (n = 48)	Non-hiccups (n = 244)	*P*-value	Odds ratio	95% CI
Cisplatin	76	32	44	<0.0001	9.09	4.59 - 18.00
Pemetrexed	21	8	13	0.0112	3.55	1.38 - 9.12
Gemcitabine	20	7	13	0.0296	3.03	1.14 - 8.06
Etoposide	31	12	19	0.0013	3.95	1.77 - 8.82

Hiccup and non-hiccup groups were compared using Fisher's exact test.

Table 5. Results of univariate analysis comparing antiemetic drugs between the chemotherapy-induced hiccup group and the non-hiccup group.

	Total	Hiccups (n = 48)	Non-hiccups (n = 244)	*P*-value	Odds ratio	95% CI
All of steroid drugs	200	48	152	<0.0001	-	-
Dexamethasone	183	44	139	<0.0001	8.31	2.89 - 23.85
Prednisolone	11	3	8	0.3982	1.96	0.50 - 7.67
Hydrocortisone	9	1	8	1	0.63	0.08 - 5.14
Methylprednisolone	2	1	1	0.3022	5.17	0.32 - 84.12
All of antiemetics	235	46	189	0.0023	6.69	1.57 - 28.45
5-HT_3 receptor antagonist	225	43	182	0.0241	2.92967	1.11 - 7.73
Metoclopramide	14	9	5	<0.0001	11.03	3.51 - 34.64

Plus-minus values are means ± SDs. Hiccup and non-hiccup groups were compared using Fisher's exact test.

medications with presence or absence of CIH as the objective variable. The results are shown in Table 7. Pain ($P = 0.0013$) and nausea and vomiting ($P <$

Table 6. Results of univariate analysis comparing drug dose between the chemotherapy-induced hiccup group and the non-hiccup group.

	Total	Hiccups (n = 48)	Non-hiccups (n = 244)	*P*-value
Cisplatin	75	103.41 ± 6.70	75.81 ± 5.63	0.0023
Pemetrexed	21	833.13 ± 25.88	756.92 ± 20.30	0.0318
Gemcitabine	19	1675.00 ± 70.49	1076.92 ± 47.89	<0.0001
Etoposide	31	157.92 ± 10.96	126.58 ± 8.71	0.0331
Dexamethasone	183	8.15 ± 0.91	9.52 ± 0.51	0.1954

Hiccup and non-hiccup groups were compared using a t-test.

Table 7. Results of univariate analysis comparing patient symptoms other than hiccups and tube insertion between the chemotherapy-induced hiccup group and the non-hiccup group.

	Total	Hiccups (n = 48)	Non-hiccups (n = 244)	*P*-value	Odds ratio	95% CI
Pain	27	11	16	0.0013	4.24	1.82 - 9.84
Nausea and vomiting	19	13	6	<0.0001	14.73	5.26 - 41.28
Constipation two days or more	21	4	17	0.7597	1.21	0.39 - 3.78
Intubation tube	1	0	1	1	0.00	-
Urinary tract	4	3	1	0.0149	16.20	1.62 - 159.24
Central venous catheter	10	3	7	0.2159	2.26	0.56 - 9.06
Peripheral venous catheter	211	26	185	0.0042	0.38	0.20 - 0.71

Hiccup and non-hiccup groups were compared using Fisher's exact test.

0.0001) were associated with CIH, and tube insertion in the urinary tract also showed an association with CIH.

No association was present between CIH and patient medications other than chemotherapy.

3.6. Multivariate Analysis

We performed multivariate analysis with CIH as a purpose variable to identify independent risk factors for CIH. The explanatory variables were those found to be associated with CIH via univariate analysis. When the square of Spearman rank-order correlation coefficient [ρ^2] was greater than 0.9, we concluded that there was an internal correlation. When there was no internal correlation, we treated these items as independent factors. The results of multivariable analysis of the 292 cases analyzed are shown in Table 8. Among physical characteristics, the male gender was identified as an independent risk factor for CIH (OR, 72.69; 95% CI, 6.95 - 757.64). In addition, the drugs cisplatin (OR, 3.84; 95% CI, 1.52 - 9.70), etoposide (OR, 3.72; 95% CI, 1.14 - 12.11), and dexamethasone (OR, 4.55; 95% CI, 1.12 - 16.91) were found to be independent risk factors. Finally, symptoms of nausea or vomiting were also found to be significant independent risk factors (OR, 52.01; 95% CI, 3.93 - 447.13).

Table 8. The result of multivariate analysis.

Risk Factors	Odds ratio	*P*-value	95% CI
Men	72.69*	0.0003#	6.97 - 757.64
Nausea and vomiting	41.94*	0.002#	3.93 - 447.13
Urinary tract	18.44	0.1883	0.24 - 1416.27
Dexamethasone	4.55*	0.0237#	1.22 - 16.91
Gemucitabine	3.95	0.1128	0.72 - 21.57
Cisplatin	3.85*	0.0044#	1.52 - 9.70
Etoposide	3.72*	0.0293#	1.14 - 12.11
Pain	3.42	0.0613	0.94 - 12.44
Pemetrexed	1.72	0.4168	0.46 - 6.38
BSA	0.37	0.51058	0.02 - 7.44

BSA, Body Surface Area (0.20247 × height $(m)^{0.725}$ × weight $(kg)^{0.425}$). * indicates a significant odds ratio. The purpose variable was the presence or absence of chemotherapy-induced hiccups. The explanatory variables were the factors independently associated with chemotherapy-induced hiccups.

4. Discussion

The present study is the first report to systematically identify risk factors for the development of chemotherapy-induced hiccups (CIH). The Musashino Red Cross Hospital is a clinical cancer therapy center with several departments. Therefore, although the study was a single-institution study, we were able to accumulate a number of cases equal to those in multi-center studies. Some previous reports of hiccups associated with chemotherapy can be found, but they have not identified suspected drugs. In the present study, we defined chemotherapy-induced hiccups (CIH) as those which occurred within one week after chemotherapy initiation, and identified factors associated with such hiccups.

Men were found to be at higher risk for CIH based on analysis of patient physical data in the present study. It has been reported that persistent or intractable hiccups occurred at a high rate in men. Lee GW *et al.* reported male predominance in peripheral hiccups, but no gender differences in hiccups occurring due to central nervous system disorders in their meta-analysis. Our results are consistent with the previous reports. Preponderance of hiccups in males has been shown in several studies, but the basis has not been clear. A study reported that difference in detection threshold in men and women may be the cause of the gender differences in hiccups [7]. It has also been suggested that CIH is a delayed drug side effect because it occurs several days after chemotherapy initiation. We considered the possibility that the gender differences in CIH may be connected to gender differences in drug absorption and metabolism. Kitraki *et al.* reported gender-based differences in specificity of steroid receptors in the brain and pituitary gland in rats [12]. In the present study, CIH occurred at an average of 1.7 ± 1.3 days after chemotherapy was initiated. Thus, CIH may be caused after a suspected drug was absorbed and metabolized.

It has been reported that cisplatin and dexamethasone were associated with CIH. Liaw *et al.* reported that more than 40% of patients experienced hiccups

after cisplatin administration [10]. Therefore, they suggested that cisplatin was a suspected cause of hiccups after chemotherapy. On the other hand, Vardy *et al.* reported that 25% of patients who had taken dexamethasone for one week after chemotherapy experienced hiccups [13], and the specific cause has not been clear. Because chemotherapy regimens use multiple drugs together, it is challenging to conclusively identify CIH causative drugs. In the present study, we systematically identified drugs associated with CIH via univariate analysis. Including drugs which were associated with a significant difference in univariate analysis, we examined the correlation between drug dose and hiccups, resulting in the identification of associations between CIH and dose of cisplatin, pemetrexed, etoposide, and gemcitabine. However, dose of dexamethasone was not found to be associated with hiccups, indicating that dexamethasone induces hiccups regardless of the dose.

We further performed multivariate analysis using significant patient characteristics, symptoms, and medications via univariate analysis and identified CIH risk factors. Cisplatin, etoposide, and dexamethasone were found to be independent CIH risk factors. Based on these results, use of cisplatin, etoposide, or dexamethasone was identified as an important suspected cause of CIH.

In the present study, 32 patients (42%) experienced hiccups among 76 patients undergoing cisplatin-containing regimens. These results are consistent with those of a previous report [10], suggesting that cisplatin-containing regimens pose a high risk for CIH compared with other chemotherapy regimens. Further, cisplatin doses had a positive correlation with hiccup onset, indicating that cisplatin may be a trigger for hiccups. The possible mechanism involved in induction of hiccups by cisplatin is stimulation of the vagus nerve due to release of serotonin because of stimulation of enterochromaffin cells [14]. An increased cisplatin dose may activate the mechanism more strongly, inducing hiccups more easily. Future studies are expected to clarify the mechanisms involved.

The association between topoisomerase inhibitors and hiccups has not been previously reported. Etoposide, a topoisomerase inhibitor, is an anti-cancer drug which induces apoptosis of cancer cells by inhibiting topoisomerases which are necessary for DNA replication [15]. It causes myelosuppression and peripheral neuropathy as side effects. Etoposide is classified as a mildly emetic drug. An association between nausea and vomiting and hiccups was found in the present study, and the emetic action of etoposide might be a possible risk factor for hiccups. We hypothesize that induction of hiccups by etoposide is not through a direct mechanism but via an indirect route involving peripheral neuropathy and digestive symptoms. Further studies are necessary to investigate this association further.

Dexamethasone has attracted attention as a possible cause of hiccups recently. Lee GW *et al.* succeeded in decreasing the induction of hiccups by changing patient medication from the antiemetic drug dexamethasone to methylprednisolone [11]. Their study suggested that hiccups occurring due to chemotherapy

were controllable by changing the steroid drug. High-dose dexamethasone passes the blood-brain barrier and activates steroid receptors in the hypothalamic hippocampus [16]. Therefore, the efferent pathway of the hiccup reflex arc is stimulated. As for the association between hiccups and steroid use, a significant difference was found only for dexamethasonevia univariate analysis. Further, dexamethasone was identified as an independent risk factor for hiccups in multivariable analysis. Analysis of correlation between drug dose and hiccups did not find an association with dexamethasone dose. Dexamethasone is an important drug in hiccup induction, and the data suggests that the hiccup-inducing effects of dexamethasone are dose-independent. Dexamethasone is often used together with an anti-cancer drug, and dexamethasone can be thought of as a factor contributing to hiccup-induced risks due to anti-cancer drugs. In particular, hiccups were induced more in combination with dexamethasone and cisplatin. In other words, a synergistic effect due to the combination of dexamethasone and anti-cancer drugs increases the risk of hiccups. We investigated the effects of drugs and doses on CIH in the present study, and this is the first report that dexamethasone increases hiccup induction by other drugs.

Regarding adverse events of hiccups, the present study showed that pain and nausea and vomiting were associated factors. Given that cancer chemotherapy is often given as adjuvant postoperative treatment, pain at wound sites may occur due to hiccups, and this may have been the basis for pain being identified as an associated factor in univariate analysis. In the multivariable analysis, only nausea and vomiting was identified as an independent risk factor for CIH. Nausea and vomiting has been reported to induce hiccups via stimulation of the pharynx posterior wall [17]. The medulla oblongata has the vomiting center, and nausea and vomiting result from afferent stimulation. It is known that the reaction center of the hiccup reflex is also in the medulla oblongata [18]. Serotonin and dopamine are neurotransmitters involved in nausea, vomiting, and hiccups as well. Nerve stimulation in nausea vomiting may have an influence on the reflex path of hiccups. The present report is the first to find that vomiting and nausea are independent risk factors for CIH. These results are likely to help understand the mechanisms involved in CIH, enabling therapy and prevention of hiccups.

The present report is also the first to examine association between tube insertion and CIH. In univariate analysis, urinary tract tube insertion was found to be associated with CIH. The urinary tract might stimulate afferent nerves and induce hiccups. However, it was not found to be an independent risk factor in multivariate analysis. We can therefore conclude no association between tube insertion and CIH.

5. Limitation

The present study was a retrospective one. We included patients who experienced hiccups after chemotherapy via searches of patient charts. Further, we investigated patient symptoms using the descriptions written by medical staff

including physicians, nurses, and pharmacists. Therefore, report bias may have been present in identifying hiccup patients and the symptoms. Because the study was a single-center investigation, this may have limited the sample. It is also important to consider selection bias because the data analyzed was that of only the patients receiving inpatient chemotherapy.

6. Conclusion

Systematic identification of CIH risk factors revealed that the most likely causative medications were dexamethasone, cisplatin, and etoposide. This is the first report that dexamethasone may increase the risk of hiccups induced due to other drugs. Further, we identified association of CIH with patient data including tube insertion and nausea and vomiting. Hiccups due to cancer chemotherapy are very unpleasant symptoms for a patient. Our findings may enable prediction of hiccups after chemotherapy, contributing to their prevention. This would lead to improvement in the quality of life of patients receiving cancer therapy.

Acknowledgements

We thank the students in the department of clinical pharmaceutics, Meiji pharmaceutical university, who made efforts in this study.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Kondo, T. (2005) Hiccup: Physiologic Backbone and the Point of the Treatment. *Journal of Clinical Anesthesia*, **29**, 225-232.

[2] Oshima, T., Sakamoto, M. and Arita, H. (1994) Hiccuplike Response Elicited by Mechanical Stimulation of Dorsal Epipharynx. *Journal of Applied Physiology*, **76**, 1888-1895. https://doi.org/10.1152/jappl.1994.76.5.1888

[3] Kondo, T., Toyooka, H. and Arita, H. (2003) Hiccup Reflex Is Mediated by Pharyngeal Branch of Glossopharyngeal Nerve in Cats. *Neuroscience Research*, **47**, 317-321. https://doi.org/10.1016/S0168-0102(03)00225-6

[4] Arita, H., Oshima, T., Kita, I. and Sakamoto, M. (1994) Generation of Hiccup by Electrical Stimulation in Medulla of Cats. *Neuroscience*, **175**, 67-70. https://doi.org/10.1016/0304-3940(94)91079-0

[5] Wilcock, A. and Twycross, R. (1996) Midazolam for Intractable Hiccup. *Journal of Pain and Symptom Management*, **12**, 59-61. https://doi.org/10.1016/0885-3924(96)00051-6

[6] Kolodzik, P.W. and Eilers, M.A. (1991) Hiccups (Singultus) Review and Approach to Management. *Annals of Emergency Medicine*, **20**, 565-573. https://doi.org/10.1016/S0196-0644(05)81620-8

[7] Lee, G.W., Kim, R.B., Go, S.I., Cho, H.S., Lee, S.J., Hui, D., Bruera, E. and Kang, J.H. (2016) Gender Differences in Hiccup Patients: Analysis of Published Case Reports and Case-Control Studies. *Journal of Pain and Symptom Management*, **51**, 278-283.

https://doi.org/10.1016/j.jpainsymman.2015.09.013

[8] Hosoya, R., Uesawa, Y., Ishii-Nozawa, R. and Kagaya, H. (2017) Analysis of Factors Associated with Hiccups Based on the Japanese Adverse Drug Event Report Database. *PLOS ONE*, **12**, e0172057. https://doi.org/10.1371/journal.pone.0172057

[9] Hayashi, M., Sugimura, H., Suga, Y., Kawahara, M., Aimiya, K. and Miyamoto, K. (2009) Study on Risk Factors for Hiccups Induced by Cisplatin-Based Chemotherapy. *Journal of Pharmaceutical Health Care and Sciences*, **35**, 89-95. https://doi.org/10.5649/jjphcs.35.89

[10] Liaw, C.C., Wang, C.H., Chang, H.K., Wang, H.M., Huang, J.S., Lin, Y.C. and Chen, J.S. (2005) Cisplatin-Related Hiccups: Male Predominance, Induction by Dexamethasone, and Protection against Nausea and Vomiting. *Journal of Pain and Symptom Management*, **30**, 359-366. https://doi.org/10.1016/j.jpainsymman.2005.08.008

[11] Lee, G.W., Oh, S.Y., Kang, M.H., Kang, J.H., Park, S.H., Hwang, I.G., Yi, S.Y., Choi, Y.J., Ji, J.H., Lee, H.Y. and Bruera, E. (2013) Treatment of Dexamethasone-Induced Hiccup in Chemotherapy Patients by Methylprednisolone Rotation. *The Oncologist*, **18**, 1229-1234. https://doi.org/10.1634/theoncologist.2013-0224

[12] Kitraki, E., Kremmyda, O., Youlatos, D., Alexis, M.N. and Kittas, C. (2004) Gender-Dependent Alterations in Corticosteroid Receptor Status and Spatial Performance Following 21 Days of Restraint Stress. *Neuroscience*, **125**, 47-55. https://doi.org/10.1016/j.neuroscience.2003.12.024

[13] Vardy, J., Chiew, K.S., Galica, J., Pond, G.R. and Tannock, I.F. (2006) Side Effects Associated with the Use of Dexamethasone for Prophylaxis of Delayed Emesis after Moderately Emetogenic Chemotherapy. *British Journal of Cancer*, **94**, 1011-1015. https://doi.org/10.1038/sj.bjc.6603048

[14] Grunberg, S.M. and Hesketh, P.J. (1993) Control of Chemotherapy-Induced Emesis. *The New England Journal of Medicine*, **24**, 1790-1796.

[15] Chen, G.L., Yang, L, Rowe, T.C., Halligan, B.D., Tewey, K.M. and Liu, L.F. (1984) Nonintercalative Antitumor Drugs Interfere with the Breakage-Reunion Reaction of Mammalian DNA Topoisomerase II. *The Journal of Biological Chemistry*, **259**, 13560-13566.

[16] De Kloet, E.R., Vreugdenhil, E., Oitzl, M.S. and Joels, M. (1998) Brain Corticosteroid Receptor Balance in Health and Disease. *Endocrine Reviews*, **19**, 269-301.

[17] Oshima, T., Sakamoto, M. and Arita, H. (1994) Hiccuplike Response Elicited by Mechanical Stimulation of Dorsal Epipharynx of Cats. *Journal of Applied Physiology*, **76**, 1888-1895. https://doi.org/10.1152/jappl.1994.76.5.1888

[18] Lee, K.H., Moon, K.S., Jung, M.Y. and Jung, S. (2014) Intractable Hiccup as the Presenting Symptom of Cavernous Hemangioma in the Medulla Oblongata: A Case Report and Literature Review. *Journal of Korean Neurosurgical Society*, **55**, 379-382. https://doi.org/10.3340/jkns.2014.55.6.379