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ORIGINAL ARTICLE

Ranitidine and the incidence of hypersensitivity reactions to paclitaxel: A retrospective cohort study

Anouk I. Haine[1] | Cornelia (Marije) A. W. Notenboom[1] | Liong (Vincent) P. Tan[2] | Rikje Ruiter[3,4] | Wendy M. van der Deure[1]

[1]Department of Internal Medicine, Groene Hart Ziekenhuis, Gouda, the Netherlands

[2]Department of Clinical Pharmacy, Groene Hart Ziekenhuis, Gouda, the Netherlands

[3]Department of Epidemiology, Erasmus Medical Center, Rotterdam, the Netherlands

[4]Department of Internal Medicine, Maasstad Ziekenhuis, Rotterdam, the Netherlands

Correspondence
Wendy M. van der Deure, Groene Hart Ziekenhuis, Gouda, The Netherlands.
Email: wendy.van.der.deure@ghz.nl

Abstract

Paclitaxel is a commonly used chemotherapeutic agent. To minimize the risk of hypersensitivity reactions (HSRs), which occur in approximately 16–42% of patients, premedication with dexamethasone, clemastine, and ranitidine was standard of care. As of October 2019, ranitidine is no longer available. We compared the risk of HSRs to paclitaxel with and without premedication with ranitidine, hypothesizing that the incidence of HSRs to paclitaxel will be similar. In this retrospective cohort study, all first-time paclitaxel users in the Groene Hart Hospital were included from January 2019 to August 2020. The primary outcome was the incidence of HSRs, using a Student's *t*-test. One-hundred and eight patients who were first-time users of paclitaxel in the Groene Hart Hospital met the inclusion criteria. Most patients were treated for breast or ovarian cancer, followed by lung cancer. Analysis of all 836 paclitaxel administrations was performed. Following 349 administrations with ranitidine as premedication, eight HSRs occurred (2.3%), while following 487 administrations without ranitidine, 12 HSRs occurred (2.5%), *p*-value of 0.87. An additional analysis on the occurrence of HSRs per patient was performed: 45 patients received premedication in the form of ranitidine, of which eight patients (17.8%) had a HSR. Sixty-three patients did not receive premedication in the form of ranitidine, of whom 10 (15.8%) had a HSR, *p*-value of .80. In conclusion, we found no difference in the incidence of HSRs during paclitaxel infusions between patients who received ranitidine as premedication versus those who did not.

KEYWORDS
H2-antagonist, hypersensitivity, paclitaxel, premedication, ranitidine

1 | INTRODUCTION

Paclitaxel is a commonly used chemotherapeutic agent. It is frequently used in the treatment of breast cancer and gynecological tumors. However, hypersensitivity reactions (HSRs), to paclitaxel and the used dissolvent cremophor EL are frequent (16 up to 42%).[1–5] The HSRs to paclitaxel almost always occur within the first hour after infusion.[6] Symptoms include dyspnoea, rash, itchiness, tachycardia, and even anaphylaxis occurs in some patients.[7,8] The reactions to paclitaxel are likely to be IgE driven and type IV hypersensitivity reactions as first-time users are affected.[6,9] To minimize the risk of these HSRs, patients are treated with premedication.[7] Based on historical

studies, ranitidine (or Zantac) was used as a standard premedication in paclitaxel administrations, in combination with dexamethasone and a H1 antagonist.[2]

However, ranitidine is not registered for the prophylaxis of HSRs and like all drug usage, is not without risk of adverse reactions like hypotension and even anaphylaxis.[10,11] The efficacy of ranitidine on preventing HSRs to paclitaxel has been debated and has not been properly analyzed since,[3] except for the study by Cox et al.[12] This study was, however, performed in an academic hospital where the study population might differ from the patient population in our hospital, therefore, our study might contribute to generalizability of the earlier found results.

In October 2019, the European Medicines Agency (EMA) raised the alarm on the possibility of forming the carcinogenic N-Nitrosodimethylamine (NDMA) during the production process of ranitidine.[13] Therefore, marketing authorization holders of ranitidine decided to recall their products leading to a worldwide shortage of ranitidine on the market. This provided an excellent opportunity to evaluate ranitidine's poorly established potential to prevent HSRs to paclitaxel. We analyzed the risk of HSRs to paclitaxel with and without premedication with ranitidine, hypothesizing that the incidence of HSR's to paclitaxel will be similar.

2 | METHODS

2.1 | Study setting

This single-center, retrospective cohort study is conducted at the Groene Hart Hospital, The Netherlands. Data on all adult (≥18 years) first-time users of one or more administrations of paclitaxel were collected. First-time users were defined as patients with no prior paclitaxel administrations. Paclitaxel administrations with and without ranitidine were compared. First-time users of paclitaxel, for all types of cancers, from January 2019 to August 2020, were included in the analyses. Users of paclitaxel monotherapy, as well as in combination with other chemotherapeutic agents, either given weekly or 3-weekly, were included in the analyses. We excluded patients with a history of ranitidine allergy or a probable history of paclitaxel usage in another hospital as well as patients who received paclitaxel with and without ranitidine, due to the recall of ranitidine in October 2019. Baseline characteristics were retrospectively collected, including age, height, length, body mass index (BMI) and body surface area (BSA), type of carcinoma, and the presence of a history of allergic reactions.

We examined reports on every paclitaxel administration that included patients received from January 2019 until the end of October 2020. We registered the number of cycles of paclitaxel that were administered, the dosages of each paclitaxel administration and whether patients had a HSR to the administration of paclitaxel. A HSR was defined as hyper- or hypotension, angioedema, flushing, generalized pruritus, hypertension, dyspnea, or chest pain during or right after paclitaxel administration.[4–6]

In the main analysis, the occurrence of a HSR per paclitaxel administration was compared for all administrations of paclitaxel with the use of ranitidine yes/no variable. Earlier research showed that first and second administrations are more likely to lead to HSRs.[6] Therefore, we performed an additional analysis, excluding patients affected by the recall of ranitidine (e.g., received two administrations of paclitaxel with ranitidine and four without). In this additional analysis, the occurrence of HSRs was compared between first-time users of paclitaxel who had received ranitidine as premedication and first-time users of paclitaxel who had not received ranitidine as premedication. The study was approved by the medical ethical committee of our Hospital.

2.2 | Statistical methods and outcome

Baseline characteristics were calculated. Using a Student's *t*-test, we compared the incidence of HSRs to paclitaxel in the presence or absence of ranitidine as a premedication drug in all administrations and in first-time users. *p*-values were considered significant if $p < .05$. All analyses were performed using R software.

3 | RESULTS

Of 125 patients who were first-time paclitaxel users in the Groene Hart Hospital, 17 patients were excluded: two because of hypersensitivity to ranitidine, two because of a history of probable paclitaxel usage in a different hospital, and 13 because they received some administrations with ranitidine and some without because of the recall of ranitidine in October 2019. Of the remaining 108 patients, 93 (86.1%) were female. The type of carcinoma for which the patients received treatment was mainly breast cancer (62.0%), followed by ovarian cancer (18.5%) and lung cancer (12.0%). The median age was 60 (interquartile range (IQR: 52–69) years), and patients had a median BMI of 25.5 (IQR: 22.7–30.1) kg/m^2 and a median BSA of 1.8 m^2 (IQR: 1.7–2.0). The majority of patients did not have a history of previous allergies $n = 66$ (61.1%). Patients received a median of 9 (minimal 1; maximum 14) administrations, with a median first dosage of 156 mg (IQR 143–299) and a median cumulative dosage of 1503 (IQR 1042–1691) mg. The baseline characteristics are shown in Table 1.

The main analysis on the incidence of HSRs per paclitaxel administration showed 836 administrations for 108 patients. Ranitidine was given as premedication in 349 of these administrations, of which eight (2.3%) led to a HSR in patients. Ranitidine was not given as premedication in 487 administrations, of which 12 (2.5%) led to a HSR. A Student's t-test comparing the incidence of HSRs in paclitaxel administration to a patient showed a *p*-value of 0.87 (Table 2).

HSRs were almost exclusively shown in patients receiving their first or second administration of paclitaxel: 22 of 25 (88%). One patient had HSRs in subsequent administrations, after which paclitaxel treatment was discontinued.

TABLE 1 Patients characteristics of patients receiving paclitaxel from January 2019 until the end of October 2020

	Total	Ranitidine	No ranitidine	*p*-value
Total number of patients	108	45	63	
Female	93 (86.1%)	40 (88.9%)	53 (84.1%)	.47
Male	15	5	10	
Primary tumor				
Breast cancer	67 (62.0%)	28	39	.97
Ovarian cancer	20 (18.5%)	10	10	.42
Lung cancer	13 (12.0%)	2	11	.03
Endometrial cancer	2 (1.9%)	2	0	
Miscellaneous[a]	6 (5.6%)	3	3	
Age (years)	60 (52–69)	63 (52–69)	63 (52–69)	.79
BMI (kg/m2)	25.5 (22.7–30.1)	25.0 (21.5–30.2)	25.6 (23.1–30.1)	.54
BSA (m2)	1.8 (1.7–2.0)	1.8 (1.7–2.0)	1.9 (1.8–2.0)	.46
Number of administrations	9 (1–14)	8 (1–14)	9 (1–12)	.97
Dosage first administration (mg)	156 (143–299)	156 (138–260)	158 (144–319)	.15
Cumulative dosage (mg)	1503 (1042–1691)	1456 (773–1690)	1539 (1089–1694)	.83
History of allergic reactions	66 (61,1%)	24 (53.3%)	42 (66.7%)	.17

[a]Miscellaneous: 3 Esophageal cancer, 2 gastric cancer, 1 bladder cancer. Numbers are median (and interquartile range IQR).

TABLE 2 Hypersensitivity reactions with and without use of ranitidine as premedication for paclitaxel

Number of:	Total	Ranitidine	No ranitidine	*p*-value
Patients	108	45	63	
Administrations	836	349	487	
Hypersensitivity reactions per administration	20 (2.4%)	8 (2.3%)	12 (2.5%)	.87
Patients with hypersensitivity reactions	18 (16.7%)	8 (17.8%)	10 (15.8%)	.80

An additional analysis on the occurrence of HSRs per patient was performed. For the additional analysis, 45 patients received ranitidine as premedication, of which eight patients (17.8%) had a HSR during one or more of their paclitaxel administrations. Sixty-three patients did not receive ranitidine as premedication. Of these 63 patients, 10 (15.8%) had a HSR during one or more of their paclitaxel administrations. The Student's *t*-test comparing the incidence of HSRs led to a *p*-value of .80 (Table 2).

4 | DISCUSSION

In this retrospective study, we analyzed the risk of hypersensitivity reactions to paclitaxel with and without ranitidine as premedication. Earlier studies showed a reduced prevalence of HSRs when ranitidine is prescribed as premedication in combination with dexamethasone.[2] Based on these findings, ranitidine has been given as premedication ever since. The percentage of HSRs in our study is in line with earlier research.[3,5,12] We found no statistically significant difference in the incidence of HSRs between patients who received premedication with ranitidine or without ranitidine.

In a recent study, similar results were found in first-time paclitaxel users in an academic hospital.[12] Our study adds to these findings as it shows similar results in a different population: academic versus non-academic patients and a higher percentage of breast and ovarian cancer. In addition, we compared baseline characteristics such as BMI, BSA, and dosage and we did not find statistically or clinically significant differences between groups. Furthermore, we looked at the occurrence of reactions to paclitaxel for all paclitaxel administrations as well as per patient. This provides a high number to analyze while also taking into consideration that reactions occur mostly in the first few administrations.[6]

These findings are sequacious when we consider the role of histamine in HSRs. As these reactions are H1 and IgE driven, it is not to be expected that a H2 receptor antagonist, which affects the regulation of gastric acid secretion, would alter the incidence of HSRs.

4.1 | Strengths and limitations

As our hospital plays a central role in the region with a diverse and sizeable patient population, we expect that this study's results are

applicable to other (non-academic) hospitals. All paclitaxel administrations are listed centrally in the pharmacy providing a complete overview of all paclitaxel users. Selection bias was therefore limited. Although this is a retrospective study, information bias regarding the occurrence HSRs is unlikely. As the outcome determinant occurs within a short timeframe after administration, it is unlikely that HSRs are missed. In our hospital, a dedicated trained team of medical professionals work with our oncology patients. We believe that the documentation of HSRs is consistent for all patients in this study. The infusion rate was adjusted for all subsequent times, if the patient had an HSRs to paclitaxel, with the aim to lower the number of HSRs in the patient. As this is common practice, we believe the effect can be disregarded.[1]

Information on ranitidine use for indications other than premedication was not registered. However, because of the recall of ranitidine, it is unlikely that there are ranitidine users in the group who did not receive it as premedication. All information was extracted from patients' files, therefore there was no recall bias. Although there was no randomization due to the study's setting, the demographic characteristics of the patients in both groups are comparable. In our hospital, lung cancer is a relatively new indication for paclitaxel treatment, which explains the increasing numbers over time.[14] However, as the primary tumor type is not associated with the occurrence of HSRs, we do not think that this will have confounded our results.[4,6]

5 | CONCLUSION

In our study, no difference was found in the incidence of hypersensitivity reactions (HSRs) following the administration of paclitaxel between patients who received ranitidine as premedication versus those who did not. As the underlying biological mechanism is debatable, and similar findings are found in different populations, our results are strengthening the hypothesis that the incidence of HSRs to paclitaxel does not depend on ranitidine. More in-depth research on the evidence for the use of dexamethasone and clemastine would be of interest.

CONFLICT OF INTEREST

The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. The authors received no financial support for the research, authorship, and/or publication of this article.

DATA AVAILABILITY STATEMENT

Research data are not available at this time.

ORCID

Anouk I. Haine https://orcid.org/0000-0003-2292-7029

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