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ORIGINAL ARTICLE

Histamine-2 (H_2) antagonists can be safely removed from standard paclitaxel premedication regimens

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Aims: The aim of this study is to investigate the rates of hypersensitivity reactions (HSRs) in patients receiving paclitaxel chemotherapy, with and without a histamine-2 (H_2) antagonists.

Method: This prospective, multi-centre, cohort study compared patients receiving paclitaxel treated with premedication regimens containing chlorphenamine, dexamethasone and an H_2 antagonist *vs* patients treated without an H_2 antagonist. Rates of HSRs were described and logistic multivariable regression was used to investigate any associations with H_2 antagonist treatment, adjusting for confounding variables.

Results: A total of 1043 individuals were included in the study; of these, 638 (61%) patients received an H_2 antagonist and 405 (49%) were not given an H_2 antagonist. Incidence of HSR in the cohort treated with H_2 antagonists was 11.31% ($n = 70$) *vs* 9.86% ($n = 41$) in the cohort without. There was no statistically significant difference between the rates of HSR observed in those receiving and not receiving an H_2 antagonist (odds ratio 1.04, 95% CI 0.65, 1.66, $P = .9$).

Conclusions: Results presented within the study are consistent with other recently published evidence to suggest that H_2 antagonists do not confer any advantage as part of premedication regimens in reducing the incidence of HSR in patients treated with paclitaxel.

KEYWORDS
chemotherapy, H_2 antagonists, hypersensitivity, paclitaxel

1 | INTRODUCTION

Paclitaxel is a chemotherapy agent that is commonly used in the treatment of many solid cancers worldwide including breast, cervical, lung, oesophageal, ovarian and pancreatic.[1] However, its use is associated with significant risk of hypersensitivity reactions (HSRs) which occurred in up to 40% of patients prior to the implementation of any premedication regimen.[1] These reported HSRs range from mild erythematous skin reactions through to severe, life-threatening anaphylaxis.[2–4]

To reduce the rate of HSRs, premedication regimens, comprising of a corticosteroid combined with **H_1** and **H_2** receptor antagonists, were introduced.[2,5–8] The constituent components of these regimens were extrapolated from contemporary clinical practice used in the prevention of HSRs in patients receiving contrast media agents for radiological investigations at the time of phase I and II paclitaxel clinical trials.[9,10] Despite such regimens being accepted as a standard of care during radiological investigation, the clinical benefit of the inclusion of H_2 antagonists has been a subject of debate, with Greenberger et al. describing comparable rates of HSRs in patients receiving the

three-agent regimen versus those treated with an H_1 antagonist and corticosteroid alone.[11,12]

Ranitidine is a H_2 antagonist which, up until recently, was widely available and therefore became an accepted standard of care within paclitaxel premedication regimens. Recently, it has been withdrawn from international drugs markets following concerns around contamination with N-nitrodimethylamine (NDMA), a ubiquitous environmental compound which has been implicated as a potential carcinogen.[13–15] This withdrawal has promoted a renewed interest in paclitaxel premedication regimens with healthcare providers forced to review established practice and consider alternative strategies.[13] This product recall has coincided with the publication of the findings of Cox et al., a pre-post, interventional, noninferiority study which described the HSR rate in patients treated with paclitaxel using premedication regimens with and without ranitidine. The results of this study demonstrated noninferiority of premedication regimens without ranitidine *vs* the traditional three-agent combination.[16]

Hospitals in the UK have adopted a range of different response strategies. These can be grouped into three distinct approaches: continuing to use ranitidine (where available), use an alternative H_2 antagonist or cease the use of any H_2 antagonists.[13,17] This divergence in practice has provided a unique opportunity to evaluate the safety of the omission of ranitidine from paclitaxel regimens and build evidence into historic standard of care practices. A service evaluation was therefore developed by members of the British Oncology Pharmacy Association (BOPA) with the key objectives being to evaluate the HSR rates in patients that received H_2 antagonists and those that did not and then to investigate any differences in occurrence of HSRs.

What is already known about this subject

- There is a weak theoretical basis for the use of histamine-2 (H_2) antagonists to prevent hypersensitivity reactions with paclitaxel chemotherapy.
- One single site study demonstrated non-inferiority when omitting H_2 antagonists from premedication regimens.
- The H_2 antagonist ranitidine was withdrawn from the international market resulting in a variation in practice where some hospitals continued to source alternative agents whereas others omitted this component of premedication.

What this study adds

- There is variation in H_2 antagonist use with paclitaxel in the UK.
- We provide evidence that there is no association between H_2 antagonist premedication and occurrence of hypersensitivity reactions in patients treated with paclitaxel.
- The evidence reported should be used to change licensing of paclitaxel, where there is a current requirement to use H_2 antagonists as part of premedication.

2 | METHODS

A multi-centre, prospective cohort study involving 14 UK hospitals was conducted. Hospitals were recruited through an open invitation sent to the membership of BOPA and the NHS chief pharmacist network, thereby providing all UK hospitals which provide oncology services with an opportunity to participate. Upon expression of interest, participating centres were supplied with an Excel-based data collection tool (developed by EF, PC and CP) alongside relevant training to gather data for all patients commencing treatment with paclitaxel. The tool was developed to facilitate meaningful analysis of potential confounding variables which were identified following review of published literature (see Table S1 in the Supporting Information). These data fields included grouped age, gender, disease diagnosis, line of treatment, paclitaxel dose, cycle number, details of co-commitment chemotherapy treatments, details of the premedication regimen administered and details of any HSRs experienced by patients. Any HSRs identified were categorised and graded in accordance with common terminology criteria for adverse events (CTCAE) v5.[18] Paclitaxel infusion rates were all concordant with standard practice, which is directly correlated to the dose administered. All hospitals collecting data confirmed that infusion rates were homogeneous. Co-commitment chemotherapy was described as any chemotherapy given alongside paclitaxel. We also requested that participating centres follow internal organisational processes regarding site-specific study approval and data-sharing agreements. To ensure conformity of data, outcomes for patients treated with paclitaxel-albumin (nab-paclitaxel) and those who received paclitaxel as part of a clinical trial, including as a phase I or II investigational medicinal product (IMP), were not included. Data were de-identified by participating centres, prior to secure transfer to a secure environment at the Royal Marsden Hospital.

2.1 | Analysis

Data were analysed using R (v 4.03). HSRs relating to H_2 antagonist use were described as counts and percentages (%) at the first cycle of treatment and Fisher's exact test was used to compare any differences. The first cycle was chosen as this would accurately reflect those patients receiving combination treatment. Logistic multivariable regression was employed to investigate the outcome of any reported HSR and identify the associations with H_2 antagonist treatment, adjusting for confounding variable. Confounding variables were limited through univariable screening, and confounders that were

clinically significant were retained in the final model using a threshold of $P < .25$. Nomenclature used in reported tables conforms with international guidance.

2.2 | Missing data

Data submitted for patients who were established on treatment before the beginning of this study were excluded from analysis. Patients who experienced more than one HSR were counted for only their first reaction to avoid presenting unrepresentative results.

2.3 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander et al., 2019 a,b).[19]

3 | RESULTS

A total of 33 hospitals responded to our initial request to collect data. Of these, 14 hospitals were able to gain the necessary internal approvals and submitted data for this evaluation.

Data for 1171 patients were collected. Upon analysis, data for 128 patients were incomplete and therefore excluded. In total, results for 1043 patients were included within the final published data (described in Table 1) of which the largest patient cohort were females with a breast or ovarian cancer diagnosis (89%). Over a third of patients had a breast cancer diagnosis where use of paclitaxel monotherapy is commonly used in the adjuvant setting.[20] A total of 638 patients received an H_2 antagonist as part of the premedication regimen with at least their first dose of paclitaxel. Twenty-nine patients (4.5%) experienced an HSR during their first cycle of treatment and 32 (5%) experienced an HSR during their second cycle. A total of 405 patients did not receive an H_2 antagonists as part of the premedication regimen, of which nine (2.1%) reacted during their first cycle and 21 (4.8%) during their second cycle. Table S2 in the

TABLE 1 Summary of patient characteristics at first dose of paclitaxel treatment

Characteristic	H_2 antagonist ($N = 638$)[a]	None ($N = 405$)[a]	*P*-value
Age			0.015[b]
<60 years	275 (43%)	144 (36%)	
≥60 years	363 (57%)	261 (64%)	
Sex			<0.001[b]
Female	598 (94%)	334 (82%)	
Male	40 (6.3%)	71 (18%)	
Diagnosis			<0.001[b]
Breast	247 (39%)	143 (35%)	
Gynaecological	193 (30%)	147 (36%)	
Lung	29 (4.5%)	53 (13%)	
Upper GI	23 (3.6%)	37 (9.1%)	
Other	146 (23%)	25 (6.2%)	
Chemotherapy combination			<0.001[b]
Combination	108 (17%)	1 (0.2%)	
No combination	530 (83%)	404 (100%)	
Dexamethasone dose			<0.001[c]
<8 mg	94 (15%)	15 (3.7%)	
8–16 mg	302 (47%)	255 (63%)	
>16 mg	241 (38%)	129 (32%)	
None	1 (0.2%)	6 (1.5%)	
Anti-histamine			0.062[c]
Chlorphenamine IV	636 (100%)	399 (99%)	
None	2 (0.3%)	6 (1.5%)	
Dose per metre squared			0.063[b]
< 100 mg/m^2	347 (54%)	244 (60%)	
≥100 mg/m^2	291 (46%)	161 (40%)	

[a] *n* (%).
[b] Pearson's Chi-squared test.
[c] Fisher's exact test.

Supporting Information describes a summary of patient characteristics according to the H_2 antagonist agent administered.

The total number, severity and rates of reactions in those receiving and not receiving an H_2 antagonist are shown in Table 2 and Table S3 in the Supporting Information describes this by agent. In addition, Table S3 demonstrates that most reactions occurred during the first two cycles of treatment. Most reactions experienced by patients were low grade (≤ grade 2) across all cohorts (cimetidine

TABLE 2 Characteristics of reactions: Reaction at any point in treatment, categorised by H_2 antagonist treatment strategy at the time of reaction. Patients who did not react are classified by their initial H_2 antagonist treatment strategy but may not have received this throughout

Characteristic	H_2 antagonist ($N = 619$)[a]	None ($N = 416$)[a]	*P*-value
Reaction at any point			0.5[b]
No reaction	549 (89%)	375 (90%)	
Reaction	70 (11%)	41 (9.9%)	
Highest grade reaction			0.7[c]
0	549 (89%)	375 (90%)	
1	5 (0.8%)	1 (0.2%)	
2	57 (9.2%)	36 (8.7%)	
3	6 (1.0%)	4 (1.0%)	
Unknown	2 (0.3%)	0 (0%)	
Dose number when first reaction occurred			0.027[c]
1	29 (41%)	9 (22%)	
2	32 (46%)	20 (49%)	
3	6 (8.6%)	5 (12%)	
4	1 (1.4%)	0 (0%)	
5	1 (1.4%)	3 (7.3%)	
6	0 (0%)	3 (7.3%)	
7	0 (0%)	1 (2.4%)	
9	1 (1.4%)	0 (0%)	

[a]*n* (%).
[b]Pearson's Chi-squared test.
[c]Fisher's exact test.

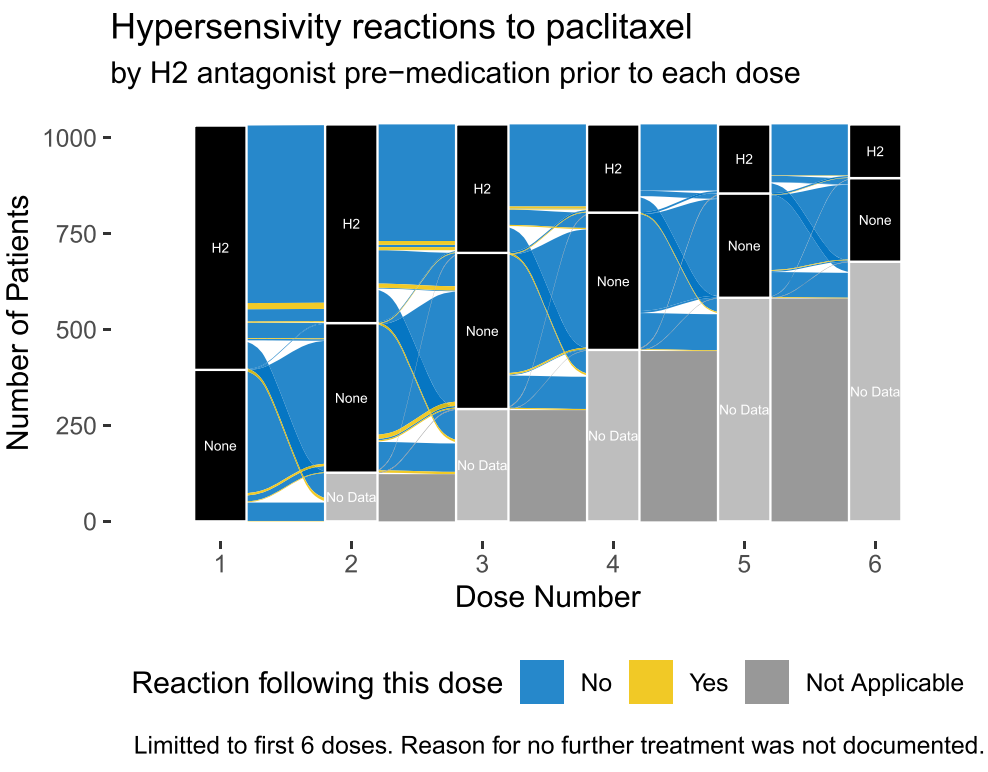

FIGURE 1 Alluvial diagram showing hypersensitivity reactions, the premedication given for that dose and the premedication given with the subsequent dose

TABLE 3 Multivariable logistic regression model

Characteristic	OR[a]	95% CI[a]	*P*-value
H_2 strategy			
H_2 antagonist	—	—	
None	1.04	0.65, 1.66	0.9
Diagnosis			
Breast	—	—	
Gynaecological	0.27	0.14, 0.48	<0.001
Lung	0.69	0.30, 1.46	0.4
Upper GI	0.77	0.28, 1.79	0.6
Other	0.62	0.33, 1.13	0.12
Chemotherapy			
Combination	—	—	
No combination	0.43	0.24, 0.80	0.006
Dose			
<100 mg/m^2	—	—	
≥100 mg/m^2	2.39	1.18, 4.70	0.013
Steroid			
<8 mg	—	—	
>16 mg	1.16	0.45, 3.20	0.8
8-16 mg	1.15	0.56, 2.57	0.7
None	1.71	0.57, 4.89	0.3

NB: Confounding variables were selected through univariable screening using a *P*-value of <.25.
[a]OR, odds ratio; CI, confidence interval.

100%, famotidine 98.5%, nizatidine 100%, ranitidine 98.3%, no H_2 antagonist 98.9%). Some centres chose to administer an H_2 antagonist as part of the premedication regimen during only the first two cycles, likely for this reason. This is further described in Figure 1, which shows the flow of patients that received an H_2 antagonist and those that did not.

In total, 111 HSRs were recorded across all cycles. Using multivariable logistic regression (Table 3), adjusting for several confounders, no association between H_2 antagonist strategy employed, and the incidence of a HSR was discerned.

4 | DISCUSSION

In this prospective multi-centre, cohort study that included 1043 patients from 14 hospitals across the UK, we found that there was no association between H_2 antagonist premedication and occurrence of HSRs in patients treated with paclitaxel. The results outlined within this study are consistent with those described in the RANISTOP trial by Cox et al. and provide further evidence to suggest that H_2 antagonists do not confer any clinical advantage in reducing the incidence of HSRs as part of a premedication regimen (odds ratio [OR] 1.04, 95% confidence interval [CI] 0.65–1.66, *vs* OR 0.55, 95% CI 0.31–0.98, $P = .043$).[16] Further to the results described in Cox et al., the results presented in this study provide evidence to suggest that this lack of effectiveness is similar across all of the H_2 antagonists included within the reported data, suggesting ineffectiveness is a class effect.

The results indicate an increased risk of HSR associated with higher doses of paclitaxel (>100 mg/m^2, OR 2.39, CI 1.18–4.70, $P = .013$). This finding builds on earlier work in the RANISTOP study where total cumulative dose of paclitaxel at the onset of HSR reaction was reported but was not included within the multivariable analyses.[16] Paclitaxel is used as a treatment option across a range of malignancies where doses and frequency of administrations vary significantly. Further investigation is required to effectively differentiate the relation between dose and frequency of administration of paclitaxel on incidence of HSR.

Evidence to describe the relationship between dose and frequency of administration may also further understanding of the impact of primary diagnosis in multivariable analysis. Published research suggests no association between tumour site and incidence of paclitaxel HSR; however, this work does not effectively differentiate the complex relationship between potential variables.[21–23] The extent of previous chemotherapy treatment received by patients prior to initiating paclitaxel may also play a role in this relationship and help to explain the results obtained within this study but has yet to be characterised and lies outside the scope of this research.

Use of ranitidine is itself associated with a 0.7% incidence of HSR, demonstrating further rationale for its removal from premedication regimens.[24,25] Indeed, the results documented by Cox et al. demonstrate an increased incidence of HSR grade 3 and above in patient cohorts who received ranitidine *vs* those that did not (4.4% *vs* 1.6%, difference −2.7% [90% CI: −6.2 to 0.1]).[16] The authors of that study acknowledge that the low number of HSR events recorded do not allow for meaningful multivariable analysis to demonstrate whether inclusion of ranitidine in premedication regimens is or is not a significant factor in explaining the results obtained. However, it is interesting to note that a similar result was described in earlier work by Greenberger et al. in patients receiving radiological contrast media, with both studies suggesting that the inherent HSR risk from ranitidine may provide some explanation for the increased incidence of HSR in patients who received ranitidine as part of a premedication regimen.[11,12]

Beyond the results obtained within this study, and those from Cox et al., the use of H_2 antagonists is no longer a standard of care in premedication regimens prior to administration of radiological dyes, with clinical practice in this area having progressed in the intervening period between the late 1980s and the present day, thus further calling into question the legitimacy of this practice in oncology.[10,26,27]

The results presented, alongside those in the RANISTOP study, demonstrate the continued effectiveness of a premedication regimen comprising chlorphenamine and dexamethasone only in reducing the incidence of paclitaxel-induced HSRs.[16] Significant research into the dexamethasone component of premedication has been conducted, providing further evidence of its efficacy across different methods of administration and dosing schedules.[28–30] While the components of paclitaxel premedication regimens were originally introduced without

a supporting evidence base, the cumulative results of this study, and a range of other published literature regarding paclitaxel premedication regimens, provides a significant post-hoc evidence base to support continued use of this two-agent combination.

This study was the largest of its kind investigating the impact of H_2 antagonists on rates of HSRs as part of premedication regimens in patients receiving paclitaxel, challenging treatments that have been established as standard of care without a rigorous evidence base. The results presented cover a cross section of UK hospitals, which we believe to be representative of wider practice across the country, and internationally. However, divergence of policies between these hospitals may have existed. Moreover, there were some differences in gender and the cancers treated in those that received an H_2 antagonist and those that did not. The results of the study are, however, consistent with those reported in the RANISTOP trial, which provides greater assurance regarding the validity of the results presented.[16]

The results outlined within this study are consistent with those described in Cox et al. and provide evidence to suggest that H_2 antagonists do not confer any clinical advantage in reducing the incidence of HSRs. Therefore we recommend that they are removed from premedication regimens given before paclitaxel treatments.[16] Current clinical trial protocols which contain paclitaxel reflect established clinical practice and commonly mandate that H_2 antagonists are included in premedication regimens; we recommend revision of this requirement.

Adoption of these recommendations in the UK is likely to be complicated by the continued inclusion of explicit reference to H_2 antagonists as a component within premedication regimens, within paclitaxel product licences, as regulated by the Medicines Health Regulatory Agency (MHRA). This requirement is mirrored in licensing decisions made by international medicines regulatory agencies, including the Food and Drugs Administration (FDA) and the European Medicines Agency (EMA). Following the results published within this study, alongside those described in Cox et al., we would invite a review of product licensing requirements from all medicines regulatory agencies to discontinue the requirement to include H_2 antagonists within premedication regimens. This is a historic, non-evidence-based practice and should be updated on the strength of contemporary published literature in this field.

The international recall of ranitidine products has seen a number of NHS hospitals switch to using alternative H_2 agents in paclitaxel premedication regimens.[13,17] This in turn has placed significant strain on supplies of alternative H_2 antagonists, which has resulted in supply shortages of these agents.[13] A review of the UK National Cancer Registration and Analysis Service (NCRAS) database in 2019, prior to the ranitidine product withdrawal, shows that 416 441 doses of ranitidine were administered as part of premedication regimens to patients receiving paclitaxel. Removal of H_2 antagonists from premedication regimens would likely alleviate a significant source of demand for alternative H_2 agents, helping to conserve supplies for other patient groups.

Furthermore, this study highlighted a significant variation in the use of H_2 antagonists within current clinical practice across the UK. This variability is concerning as it illustrates an absence of a clear, consistent approach following the impact of the withdrawal of ranitidine. The data provided from participating centres suggests that a number of NHS organisations continue to use ranitidine nearly 2 years after its withdrawal from the market as a direct consequence of concerns over contamination with a known carcinogen. The continued inclusion of ranitidine as part of the premedication regimen requirements within the paclitaxel product licence, while ranitidine has simultaneously been withdrawn from the market, has presented NHS hospitals with a lack of clarity around how to effectively manage this complex issue. The results published within this study, alongside those of Cox et al., present evidence to reframe initial risk–benefit estimations and suggests that this practice now presents an unacceptable risk to patient safety.

5 | CONCLUSIONS

The results published within the study demonstrate that H_2 antagonists are ineffective in reducing the incidence of HSRs as a component of premedication regimens in patients treated with paclitaxel and therefore recommend removal from paclitaxel product licences and policies recommending the premedication.

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COMPETING INTERESTS

Emma Foreman declares consultancy for Ipsen and Bristol Myers Squibb, outside the submitted work. Callum Polwart declares no conflicts of interest. Andrew Walker declares no conflicts of interest. Pinkie Chambers reports research grants from Janssen, Pfizer, Tessaro and Bristol Myers Squibb, outside the submitted work.

CONTRIBUTORS

All authors conceived and planned the research. E.F. is the named Principal Investigator and conducted the data collection and C.P. and

P.C. performed all analysis. All authors contributed to the interpretation of the results. A.W. took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript.

DATA AVAILABILITY STATEMENT

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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