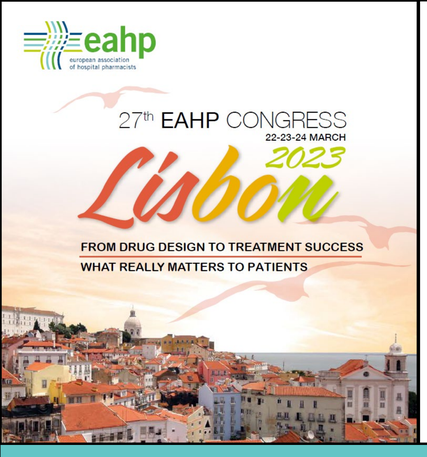

IMPACT OF HISTAMINE-2 ANTAGONIST SHORTAGE ON THE INCIDENCE OF HYPERSENSITIVITY REACTIONS TO PACLITAXEL – TOWARDS CRISIS MANAGEMENT AND A PREMEDICATION RECONSIDERATION IN FRANCE (PACLIREACT STUDY)

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BACKGROUND AND IMPORTANCE

At the beginning of October 2019, an international shortage of ranitidine forced us to adjust paclitaxel-based chemotherapy premedication regimens. After several modifications, we implemented an anti-allergic premedication protocol based on Dexchlorpheniramine as histamine-1 antagonist (H1A), double dose of Methylprednisolone at first injection as corticosteroid (CS) and withdrawal of histamine-2 antagonists (H2A).

AIM AND OBJECTIVES

This study aimed to determine the efficacy of this modified regimen and assess the hypersensitivity reactions (HSRs) associated with it.

MATERIEL AND METHODS

We conducted a single-center observational retrospective study of paclitaxel administrations (7173 administrations in 831 patients). All incidents characterized as drug allergies in the prescribing software were exhaustively recorded over a two-year period from January 2019 to December 2020 (before and after ranitidine shortage, including the period with oral Famotidine as a transitional alternative). To model the risk of allergy at each injection according to the type of injection and possible confounding factors, a mixed logistic regression model was implemented to account for repeated administration per patient. Injections without H1A or steroid premedication (n = 27) were excluded from the analysis. The model was implemented on a total of 7146 injections, of which 27 HSRs were noted. The level of statistical significance was set at $p < 0.05$, using two-sided tests.

RESULTS

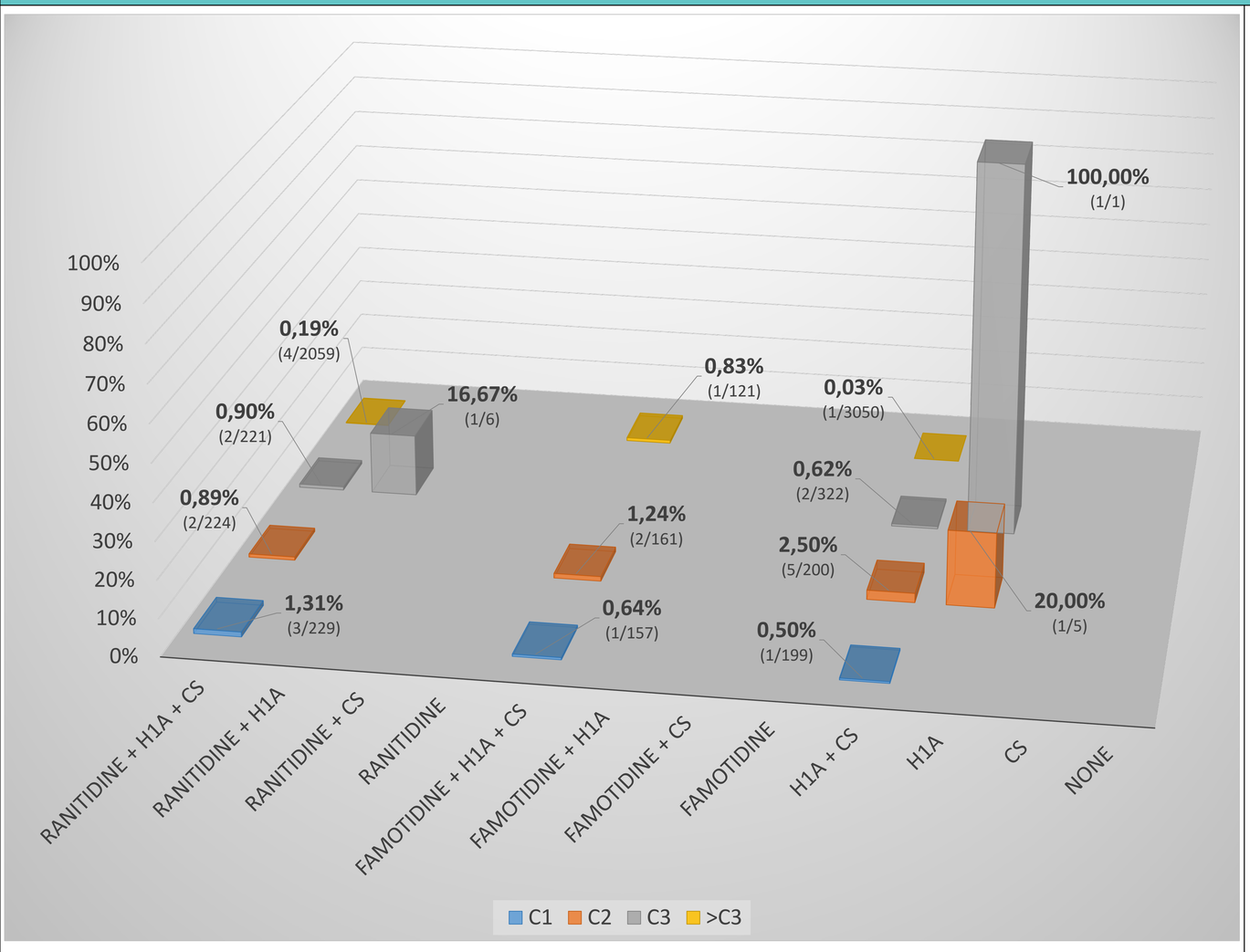

Figure 1 : Proportion of hypersensitivity reactions based on premedication protocol and paclitaxel injection number

	n/N	Odds Ratio	95% Confidence interval	*p*-value
H2A				0.94[a]
No H2A	11/3868	1 (ref)		
Famotidine	4/472	0.95	0.18–4.91	
Ranitidine	12/2806	1.21	0.35–4.21	
Corticosteroids (CS)				0.03
No	3/149	1 (ref)		
Yes	24/6997	0.08	0.008–0.78	
Injection number				0.0003[b]
Injection n°1	5/622	5.14	1.14–23.2	
Injection n°2	10/599	16.7	4.4–62.8	
Injection n°3	6/577	10.6	2.6–42.7	
Injection n°4 or more	6/5348	1 (ref)		

All results are estimated by multivariate analysis, including the three covariates listed in the model and considering the patient as a random effect.
[a] When testing H2A Yes (famotidine or ranitidine) versus No, OR:1.12, 95% CI:0.36–3.50, $p = 0.84$; when testing famotidine versus ranitidine, OR:0.788, 95% CI:0.1–4.3, $p = 0.78$
[b] When comparing the risk associated with the first three injections compared to the subsequent injections, OR:10.1, 95% CI: 3.23–31.4, $p < 0.001$; when comparing the risk associated with the 2nd injection compared to all other injections, OR:5.71, 95% CI:1.98–16.44, $p = 0.001$

Table 1 : Results of the mixed logistic regression (multivariate analysis)

Among the 7146 paclitaxel administrations, there were a total of 27 HSRs occurring in 24 patients, among whom three patients had two consecutive events. No protective effect was observed for H2A premedication regimens, neither when comparing the two types of H2A (famotidine or ranitidine) separately (p = 0.94) nor when comparing injections with H2A premedication versus injections without H2A (OR: 1.12, 95% CI, 0.36-3.50, p = 0.84).
However, the risk of HSRs was significantly lower for paclitaxel injections with corticosteroids than for those without corticosteroids (OR: 0.08, 95% CI: 0.008-0.78, p = 0.03).
In addition, the risk of HSR was significantly higher for the first, second, or third paclitaxel injections than for the subsequent injections (OR: 10.1, 95%CI: 3.23-31.4, p < 0.001).

CONCLUSION AND RELEVANCE

This study did not find evidence of an increased risk of HSR owing to the absence of H2A in the premedication protocols for paclitaxel. We have also shown that oral famotidine does not appear to be a better alternative to intravenous ranitidine. This is probably due to the administration scheme, which is compliance-dependent on home administration schedules that are difficult to meet in an outpatient setting, with possible delays. Corticosteroids have a major role in the prevention of HSR and increasing their dose for the first 2 injections could be interesting. Therefore, we hypothesize that H2A premedication prior to paclitaxel may have limited use in the prevention of HSR, despite what is historically stated in Paclitaxel monographs. These results are consistent with the literature[1,2]. Paclitaxel premedication regimens should be reviewed.

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2. *Cox JM, van Doorn L, Malmberg R, Oomen-de Hoop E, Bosch TM, van den Bemt PMLA, et al. The added value of H2 antagonists in premedication regimens during paclitaxel treatment. Br J Cancer. 2021 May;124(10):1647–52.*

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L01- ANTINEOPLASTIC AGENTS