REFERENCES

1 Savarese G, Lund LH. Global public health burden of heart failure. *Card Fail Rev* 2017;**3:**7–11.
2 Huffman MD, Prabhakaran D. Heart failure: Epidemiology and prevention in India. *Natl Med J India* 2010;**23:**283–8.
3 Harikrishnan S, Jeemon P, Ganapathi S, Agarwal A, Viswanathan S, Sreedharan M, *et al*. Five-year mortality and readmission rates in patients with heart failure in India: Results from the Trivandrum heart failure registry. *Int J Cardiol* 2021; **326:**139–43.
4 Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, *et al*.; Authors/Task Force Members; Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18:**891–975.
5 Tat V, Forest CP. The role of SGLT2 inhibitors in managing type 2 diabetes. *JAAPA* 2018;**31:**35–40.
6 Pradhan A, Vohra S, Vishwakarma P, Sethi R. Review on sodium-glucose cotransporter 2 inhibitor (SGLT2i) in diabetes mellitus and heart failure. *J Family Med Prim Care* 2019;**8:**1855–62.
7 McGuire DK, Shih WJ, Cosentino F, Charbonnel B, Cherney DZI, Dagogo-Jack S, *et al*. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: A meta-analysis. *JAMA Cardiol* 2021;**6:**148–58.
8 Lopaschuk GD, Verma S. Mechanisms of cardiovascular benefits of sodium glucose co-transporter 2 (SGLT2) inhibitors: A state-of-the-art review. *JACC Basic Transl Sci* 2020;**5:**632–44.
9 McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, *et al*. DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;**381:** 1995–2008.
10 Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, *et al*; SOLOIST-WHF Trial Investigators. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med* 2021;**384:**117–28.
11 Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, *et al*; PARAGON-HF Investigators and Committees. Angiotensin-neprilysin inhibitor in heart failure with preserved ejection fraction. *N Engl J Med* 2019; **381:**1609–620.
12 Nassif ME, Windsor SL, Borlaug BA, Kitzman DW, Shah SJ, Tang F, *et al*. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: A multicenter randomized trial. *Nat Med* 2021;**27:**1954–60.
13 Koufakis T, Mustafa OG, Tsimihodimis V, Ajjan RA, Kotsa K. Insights into the results of sotagliflozin cardiovascular outcome trials: Is dual inhibition the cherry on the cake of cardiorenal protection? *Drug* 2021;**81:**1365–71.
14 McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al*; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;**42:**3599–726.
15 McMurray JJV, Packer M. How should we sequence the treatments for heart failure and a reduced ejection fraction?: A redefinition of evidence-based medicine. *Circulation* 2020;**143:**875–77.

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H2 blockers in the prevention of paclitaxel-related hypersensitivity reaction

Cox JM, van Doorn L, Malmberg R, Oomen-de Hoop E, Bosch TM, van den Bemt PM, Boere IA, Jager A , Mathijssen Ron HJ, van Leeuwen Roelof WF. (Department of Clinical Pharmacy and Maasstad Lab, Maasstad Hospital, Rotterdam; Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam; Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam; Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Groningen; Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam—all in the Netherlands.) The added value of H2 antagonists in premedication regimens during paclitaxel treatment. *Br J Cancer* 2021;**124:**1647–52.

SUMMARY

Dexamethasone and histaminic (H1 and H2) blockers are routinely used as pre-medication drugs for the paclitaxel-related hypersensitivity reaction (HSR). The inclusion of this strategy was more empirical than evidence-based following the initial experience with life-threatening HSR during phase 1 studies done in early 1981.[1] The inclusion was to reciprocate the prevention strategy similar to contrast-induced HSR.[2] People worldwide continued to use the same preventive measures over the past 40 years. Of the three components of a preventive strategy, the most argued one is the role of H2 receptor antagonists.[3] We congratulate Cox *et al*. for raising and successfully testing the research question. However, they selected a pre–post interventional study. A randomized study design is a preferred scheme to get a value close to the true one. In this study, steroids and clemastine (H1 blockers) were given with or without ranitidine (H2 blockers) during October 2018 to April 2019 and April to December 2019. The study design was an open-labelled, non-randomized, non-inferiority trial. The trial enrolled adult patients (18 years or above) who were to receive the first cycle of conventional paclitaxel (weekly or three-weekly, with or without partner drug) for a maximum of six cycles. The primary end-point was the incidence of grade 3 or more HSR. The sample size was 366 with a 6% non-inferiority margin, 90% power and a one-sided alpha error of 0.05. The common tumour type was oesophagus (42%), breast (32%), lung (9%) and gynaecological (14%). In both the arms, an equal proportion of patients received corticosteroids (9.8%) and antihistamines (4.95) for other associated comorbid conditions. In the two study arms with and without ranitidine, the rate of all grades HSR was (20% *v.* 12%), grade 3 or higher HSR (4.4% *v.* 1.6%) and grade 1–2 HSR (16% *v.* 10%).[4] The difference between the two arms was –2.7% (90% CI –6.2% to 0.1%). The present study concluded that ranitidine (H2 blocker) can be safely omitted from the standard paclitaxel pre-medication strategy.

COMMENT

It is good to see a real-life, simple question being addressed, which has remained neglected for the past four decades. Although ranitidine is a cheap drug, its routine use with paclitaxel (one of the most commonly used chemotherapy drugs) adds cost to cancer care. Interestingly, the rate of severe

(4.4% *v.* 1.6%) and all grade HSR rates (20% *v.* 12%) were numerically lower in the arm without ranitidine. The data presented provide reassurance to safely omit H2 blockers. Ranitidine is associated with a HSR, hepatotoxicity, nephrotoxicity and thus omission of unnecessary use is welcome.[5–7] Lately, ranitidine has been associated with cancer risk due to contamination with a chemical called N-Nitrosodimethylamine (NDMA). The discovery of ranitidine containing a high level of NDMA led to the US Food and Drug Administration announcing holding its sales across the USA.[8] Similar regulations were implemented in Canada and France. It is not clear whether it is related to contamination or part of drug decomposition. However, in India, the drug is not banned and is commonly used for the prevention of paclitaxel-induced HSRs. Avoiding the unnecessary use of ranitidine carries the potential to reduce both the cost and the side-effects. However, we believe that several issues require clarification before a change in practice.

The study design has a few limitations. A randomized, blinded, placebo-controlled trial would have been the best to provide evidence to change the present practice. However, this study was a single-centre, non-randomized, open-label study. The study design thus has a potential for various forms of bias. The rate of all and severe grade HSRs vary markedly in the published literature (2%–45%).[2,9,10] In the study, the rate of all grade HSR rate was almost half in the ranitidine arm, which cannot be explained. There is no well-defined prospectively evaluated identifiable risk factor for paclitaxel HSR. Thus, a non-randomized study has a high potential for unbalanced allocation of unknown confounding factors between the two arms. The study did not provide details of the HSR in the weekly and three-weekly arms. There was a higher proportion of gynaecological cancer in the ranitidine arm (19.1% *v.* 8.1%). Gynaecological cancer was associated with the severe form of HSR on the univariate analysis. Although no comparative randomized data exist, retrospective studies suggest a higher rate of paclitaxel-related HSR with the three-weekly regimen.[11]

Hence, we consider the study as hypothesis-generating given the above-mentioned limitations and suggest caution against the omission of H2 receptor blocker (ranitidine) as part of the paclitaxel pre-medication strategy. Similar studies with a large sample size will generate confidence among clinicians. This study has encouraged us, and we have planned a phase 3, randomized, blinded, placebo-controlled, parallel assigned, with non-inferiority study design at our centre to answer the study question in a more rational and well-controlled setting and to gain experience at the same time.

Conflicts of interest. None declared

REFERENCES

1 Wiernik PH, Schwartz EL, Einzig A, Strauman JJ, Lipton RB, Dutcher JP. Phase I trial of taxol given as a 24-hour infusion every 21 days: Responses observed in metastatic melanoma. *J Clin Oncol* 1987;**5:**1232–9.
2 Rowinsky EK, Donehower RC. Paclitaxel (taxol). *N Engl J Med* 1995;**332:** 1004–14.
3 Slimano F, Coliat P, Perotin JM, Vella-Boucaud J, Mongaret C, Bouché O. Is antihistaminergic H2 really useful in prevention of hypersensitivity induced by paclitaxel? *Support Care Cancer* 2016;**24:**4475–7.
4 Cox JM, van Doorn L, Malmberg R, Oomen-de Hoop E, Bosch TM, van den Bemt PM, *et al*. The added value of H2 antagonists in premedication regimens during paclitaxel treatment. *Br J Cancer* 2021;**124:**1647–52.
5 Aouam K, Bouida W, Ben Fredj N, Chaabane A, Boubaker H, Boukef R, *et al*. Severe ranitidine-induced anaphylaxis: A case report and literature review. *J Clin Pharm Ther* 2012;**37:**494–6.
6 Bossi A, Romeo G, Pezzoli A. Side-effects, structure, and H2-receptor antagonists. *Lancet* 1992;**339:**1366.
7 Fisher AA, Le Couteur DG. Nephrotoxicity and hepatotoxicity of histamine H2 receptor antagonists. *Drug Saf* 2001;**24:**39–57.
8 Commissioner O of the. FDA requests removal of all ranitidine products (Zantac) from the market. FDA; 2 Apr 2020. Available at *www.fda.gov/news-events/press-announcements/fda-requests-removal-all-ranitidine-products-zantac-market* (accessed on 2 Jun 2021).
9 Chen FC, Wang LH, Zheng XY, Zhang XM, Zhang J, Li LJ. Meta-analysis of the effects of oral and intravenous dexamethasone premedication in the prevention of paclitaxel-induced allergic reactions. *Oncotarget* 2017;**8:**19236–43.
10 Weiss RB, Donehower RC, Wiernik PH, Ohnuma T, Gralla RJ, Trump DL, *et al*. Hypersensitivity reactions from taxol. *J Clin Oncol* 1990;**8:**1263–8.
11 Premedication strategy for paclitaxel, still an unsolved question after 30 years. *Belgian J Med Oncol* 2017;**11:**46–55.

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