Ranitidine shortages following international recall: implications on pre-medication regimens to prevent hypersensitivity reactions for oncology treatments

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Ranitidine has become an establish feature in pre-medication regimens intended to reduce the risk of hypersensitivity reactions to a variety of chemotherapy agents. The ongoing supply issues with ranitidine and alternative H2 antagonists has led to healthcare providers reviewing these pre-medication regimens and adopting alternative strategies to reduce the risk to patients. This article sets out to review the background to the supply issues with ranitidine, provide a brief review of the published evidence base around its inclusion as a component in pre-medication regimens, consider the potential implications to practice in terms of the management strategy options and the need for greater understanding around the its true value in reducing the risk to patients.

Background to the recall

In October 2019 the Department of Health and Social Care issued a supply disruption alert informing healthcare providers in the UK that all oral formulations of ranitidine were likely to be out of stock for an extended period of time[1] This announcement was made following an investigation of ranitidine-containing products by several international regulatory agencies including the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) following reported contamination with low levels of a potentially carcinogenic compound[2,3] This announcement was followed by additional alerts throughout 2019 and into 2020 which extended the remit to cover all ranitidine-containing formulations, which have now been unavailable on the international market for a prolonged period. The shortage has had an impact on the provision of care to patients across multiple specialities, including those who are undergoing treatment for malignant disease.

In October 2019 the US-based independent laboratory investigation service Valisure submitted a citizen petition to the FDA raising concerns that batches of ranitidine products, which had been subjected to analysis, had been found to contain N-nitrosodimethylamine (NDMA).[4] The same compound has previously been isolated in valsartan-containing products produced by Novartis in 2018 and led to an MHRA and FDA recall in July[5,6] then in valsartan products from other manufacturers which were also recalled and was later identified in irbesartan and losartan which was subject to recall in January and February 2019.[7]

NDMA has been classified as a probable carcinogen by the International Agency for Research on Cancer[8] and the World Health Organisation.[9] Based on the results of animal model studies, NDMA promotes tumour formation primarily in tissues in the gastrointestinal tract and liver and, less frequently, in the lungs and kidneys.[10,11] Nitrosamine chemical continuants, including NDMA, have been demonstrated to activate RAS oncogene pathways thereby promoting malignant conditions.[12] In addition to its primary carcinogenic potential, enzymatic metabolism of NDMA by CYP2E1 has been shown to result in the formation of methyldiazonium, a chemical inducer of methylation which promotes DNA point mutations, thereby conferring a systemic carcinogenic risk.[13]

The risk that NDMA poses to human health based on the levels of contamination which have been detected in ranitidine products have been the subject of some debate in the scientific community.[14] NDMA is a ubiquitous environmental chemical contaminant found in air, water, soil in trace amounts with estimated average daily intake being around 1 microgram.[16] The initial assessments conducted by Valisure on ranitidine containing products reported NDMA contamination in excess of 3 million nanograms per tablet thereby exceeding the FDAs acceptable daily intake limit of 96 nanograms.[4] However, these results were generated from samples which were subject to conditions beyond those that could be reasonably expected during manufacturing, transportation, storage or ingestion thereby introducing potential limitations around the accuracy in real-world conditions. As part of the analysis technique, samples of ranitidine products were heated to 130°C, a process which is known to increase the NMDA levels though heat-activated chemical degradation pathways in molecules which contain nitrile and dimethylamine group, such as ranitidine.[17] To address the potential unrepresentative nature of the results published by Valisure, the FDA shared guidance around alternative

analysis methods recommending liquid chromatography–high resolution mass spectrometry (LC-HRMS) or liquid chromatography–tandem mass spectrometry (LC-MS) with manufactures to assist the pharmaceutical industry to report NDMA levels achieved via standardised analysis techniques.[16]

While initial FDA testing of several ranitidine-containing products achieved results which indicated NDMA levels similar to those found in common food, such as smoked or grilled meats,[18] several pharmaceutical manufacturers announced voluntary product recalls as a precautionary measure. In the UK the MHRA announced voluntary recalls for products from a number of manufacturers through October and November 2019 and into 2020 while the extent and potential impact of NDMA contamination is assessed and regulatory agencies provide further guidance. The impact of manufacturer led recalls has resulted in a lack of available ranitidine products on the international pharmaceutical market. In the UK, the Department of Health and Social Care have issued a number of supply alerts around ranitidine formulations advising healthcare providers of the extent and duration of the shortages and providing recommendations around alternative treatments.[1,18] Lack of available ranitidine products has impacted on patient care across a range of treatment groups but has had a significant effect on patients undergoing treatment for malignant disease where it is used as a pre-medication to reduce incidence of reactions to chemotherapy or as part of a desensitisation regimen.[19]

H2 antagonists in pre-medication regimens

Ranitidine is primarily used as a premedication for paclitaxel-containing regimens, but can be included in other regimens, such as those containing other taxanes and/or those containing platinum-based agents, which carry a risk of hypersensitivity reactions.[20] Paclitaxel is a chemotherapy agent from the taxane family used to treat a range of malignant conditions including tumours which arise in ovarian, breast, lung cervical and pancreatic tissues. It exerts activity through stabilisation of tubulin mitotic spindle assembly thereby inhibiting progression of mitosis and promoting apoptosis. Paclitaxel is associated with a significant risk of hypersensitivity reactions with initial clinical trial data demonstrating a reaction rate of up to 40%.[21] To address the potential for treatment-limiting hypersensitivity reactions healthcare providers implemented pre-medication regimens with a combination of corticosteroids and antihistamines (both anti-H1 and H2), which has reduced incidence of hypersensitivity reactions to <3%.[22]

Given the success of reducing the incidence of hypersensitivity reactions with other appropriate pre-medications, ranitidine has become as an established component of paclitaxel-containing chemotherapy regimens where it is utilised for its H2 antagonist properties.[21,22] The recent shortages of ranitidine products have forced healthcare providers to consider alternative courses of action to ensure the safe and effective use of paclitaxel-containing regimens and other regimens where it has also been added as a pre-medication. In the UK, the British Oncology Pharmacists Association (BOPA) has compiled guidance to assist healthcare providers in determining the most appropriate strategies to manage the situation.[23] This guidance advocates a variety of strategies including rationalising use of ranitidine, using alternative H2 antagonists to replace ranitidine in pre-medication regimens and considering the risk of removing H2 antagonists from regimens altogether.

Rationalising or restricting access to stock based on clinical requirement is a common response from healthcare providers in the UK and internationally in times of product shortages.[24] This response helps to support the prioritisation of remaining medication and, hopefully, to maintain supply to the highest risk patient groups until restriction can be lifted and normal provision recommenced. In the case of the ongoing ranitidine shortage, this approach has allowed many healthcare providers to maintain supply to oncology services for a number of months with many switching between IV and oral formulations based on remaining local supplies. However effective this approach may prove, it is clear that rationalising use of ranitidine cannot last indefinitely. Given the length of the ongoing shortage, which is now greater than 12 months at the time of publication of this article, it is likely that many healthcare providers have now exhausted any remaining supplies meaning they will have had to adopt alternative strategies.

Management strategies and overview of published evidence

There are a variety of alternative H2 antagonist medication available which may provide a similar effect to ranitidine as part of the pre-medication regimen. Published evidence to establish the safety and efficacy of these alternative agents in chemotherapy pre-medication regimens is limited but has provided some data to support use given the ongoing ranitidine shortage. A small-scale study of patients receiving paclitaxel for gynaecological cancers suggests comparable rates of hypersensitivity reactions for patients treated with famotidine as part of a pre-medication regimen to those treated with ranitidine.[25] Other similar small-scale studies have suggested that regimens containing cimetidine and nizatidine provide similar levels of efficacy against hypersensitivity reactions.[27]

The results provided by these studies are limited due to lack of standardisation of the non-H2 antagonist elements of the regimens described and by the small sample sizes. No comparative head-to-head studies between different H2 antagonists as part of pre-medication regimens for chemotherapy have been published to establish superiority of any particular H2 antagonists to inform practice at a national or local level. A Cochrane review of ranitidine and cimetidine in the treatment of urticaria also failed to establish superiority due to lack of high-quality published evidence.[28] Published evidence regarding secondary considerations, such as the impact of different H2 antagonists (ranitidine, famotidine and cimetidine) on the metabolism of paclitaxel has concluded that there is little impact on the pharmacological and toxicity profile between these agents (29). Wider consideration should be made when reviewing alternative H2 antagonists to minimise the impact that potential drug interactions, particularly when using potent CYP450 enzyme inhibitors such as cimetidine, on patients' chemotherapy treatment and other regular medications for non-malignant conditions which can limit the choice of premedication agents.

The availability of alternative H2 antagonist agents following international recall of ranitidine has also presented a barrier to

their widespread adoption as part of premedication regimens. In the UK, the Department of Health have included updates around the availability of famotidine, cimetidine and nizatidine in a number of medicine supply notification in 2019 and 2020, informing healthcare providers of limited stock within the UK market.[1,18] The guidance issued by BOPA provides healthcare providers with advice around switching to alternative H2 antagonists but does suggest that organisations may find challenges in obtaining stock in sufficient quantity to make a long-term switch a viable option while ranitidine products remain unavailable.[23]

Given the challenges of locating suitable alternatives many healthcare providers have been left with limited choices other than to consider administering chemotherapy with a pre-medication regimen without an H2 antagonist component. Published evidence defining the impact of H2 antagonists on rates of hypersensitivity reactions from chemotherapy regimens is limited and conducted in relatively small, non-randomised studies or case reports. The lack of high-quality published data has made interpretation of the impact of ranitidine on the rates of hypersensitivity reactions across different chemotherapy agents problematic and is a longstanding issue within the field of oncology. In the UK, ranitidine has generally been restricted to paclitaxel-containing regimens, which has the strongest evidence base, and from the lack of evidence for other chemotherapy agents,[21] although local treatment centres may choose to adopt ranitidine based on preferences of clinicians. International practice is more variable with ranitidine being employed as a pre-medication in chemotherapy regimens which include taxanes, platinum-based compounds, monoclonal antibodies and immunotherapy agents.

Larger reviews conducted into hypersensitivity reactions following administration of radiocontrast media by Greenberg et al[30] suggest that H2 antagonists may not provide additional benefit to patients as part of a pre-medication regimen, casting doubt as to the value of these agents in pre-medication regimens altogether. In a review of 857 cases of hypersensitivity reactions following administration of radiocontrast media, a combination of prednisolone, diphenhydramine and ephedrine successfully reduced the rate of hypersensitivity reaction from 10.8% to 5% while the addition of cimetidine was associated with a reaction rate of 14%, although it should be noted these results were obtained from a smaller sample size of 100 patients which may limit the reliability.[30] Retrospective studies in patients receiving paclitaxel as part of breast cancer treatment regimens by Berger et al described the impact of discontinuing pre-medications entirely for all cycles following patients' second dose. In two studies, Berger et al demonstrated that discontinuing pre-medications post second cycle does not adversely impact on the rate of hypersensitivity reaction for patients receiving paclitaxel[31,32] providing evidence to support an alternative management strategy not currently described in the BOPA guidance.

The ongoing international shortage of ranitidine and alternative H2 antagonists has had an impact on the manner in which healthcare providers manage premedication regimens intended to reduce the rate of hypersensitivity reaction following administration of chemotherapy. In the UK, BOPA have advocated a variety of strategies to help hospitals to safely manage the shortage and reduce the potential risk to patients. As the duration of the shortages continue, the true impact on rates of reported hypersensitivity reactions are likely to become more apparent as healthcare providers are more likely to exhaust alternative approaches and adopt management strategies which remove H2 antagonists from pre-medication regimens entirely. While the true value of H2 antagonists remains an area of debate, it is clear that further research to characterise the impact that they have, separate from the wider cocktail of pre-medications, is important to inform evidence-based practice. To this end, BOPA intend to conduct a national service evaluation to assess the impact of removal of H2 antagonist across the UK and Ireland which will provide further evidence to identify the place and impact of H2 antagonists in pre-medication regimens.

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Declaration of interests

The authors have no interests to declare.

References

1. Department of Health & Social care. Supply disruption alert. SDA/2019/005. Ranitidine: all formulations - supply disruption alert. Issued 15/10/2019. [online] available from: https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=102904
2. U.S. Food & Drug Administration. FDA statement. Statement alerting patients and health care professionals of NDMA found in samples of ranitidine. Issued 13/9/2019. [online] available from: https://www.fda.gov/news-events/press-announcements/statement-alerting-patients-and-health-care-professionals-ndma-found-samples-ranitidine
3. European Medicines Agency. EMA to review ranitidine medicines following detection of NDMA. Issued 13/9/2019. [online]. Available from: https://www.ema.europa.eu/en/news/ema-review-ranitidine-medicines-following-detection-ndma
4. Valisure News. Valisure detects NDMA in ranitidine. Issued 13/9/2019. [online]. Available from: https://www.valisure.com/blog/valisure-news/detection-of-ndma-in-raniditine/
5. Medicines & Healthcare products Regulatory Agency (MHRA). Drug alert – class 1 medicines recall. EL (18)A/11. [online]. Issued 10/7/2018. Available from: https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=102774
6. U.S. Food & Drug Administration. FDA announces voluntary recall of several medicines containing valsartan following detection of an impurity. Issued 13/7/2018. [online]. Available from: https://www.fda.gov/news-events/press-announcements/fda-announces-voluntary-recall-several-medicines-containing-valsartan-following-detection-impurity
7. U.S. Food & Drug Administration. FDA statement. FDA updates and press announcments on angiotensin II receptor blocker (ARB) recalls (Valsartan, Losartan, and Irbesartan). Issued 28/2/2019. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan
8. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans. Overall evaluations of carcinogenicity: an updating of IARC Monographs Volumes 1-42. 1987. [online]. Available from: https://monographs.iarc.fr/wp-content/uploads/2018/06/Suppl7.pdf

9. World Health Organisation. Concise international chemical assessment document 38. N-Nitrosodimethylamine. 2002. [online]. Available from: https://www.who.int/ipcs/publications/cicad/en/cicad38.pdf?ua=1
10. Magee PN, Barnes JM. The production of malignant primary hepatic tumors in the rat by feeding dimethylnitrosamine. British Journal of Cancer. 1956;10:114–122. [online]. Available from: https://europepmc.org/article/med/13342328
11. De Stefani E. et al. Dietary nitrosodimethylamine and the risk of lung cancer: a case-control study from Uruguay. Cancer Epidemiology, biomarkers & Prevention. 1996; 5(9):679-82. [online]. Available from: https://pubmed.ncbi.nlm.nih.gov/8877057/
12. Belinsky SA, et al. Role of DNA methylation in the activation of proto-oncogenes and the induction of pulmonary neoplasia by nitrosamines. 1990. 233 (1); 105-16. [online]. Available from: https://www.sciencedirect.com/science/article/pii/002751079090155W
13. Tricker, AR. Preussmann, R. Carcinogenic N-nitrosamines in the diet: Occurrence, formation, mechanisims and carcinogenic potential. Mutation research/genetic toxicology. 1991. 259(3) 277-89. [online]. Available from: https://pubmed.ncbi.nlm.nih.gov/2017213/
14. Adamson, RH. Chabner, BA. The finding of N-nitrosodimethylamine in common medicines. The Oncologist. 2020. 25(6); 460-62. [online]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7288647/#onco13312-bib-0004
15. Fristachi, A. Rice, G. Estimation of the total daily oral intakeof NDMA attrituable to drinking water. Journal of Water Health. 2007. 5(3); 341-55. [online]. Available from: https://pubmed.ncbi.nlm.nih.gov/17878549/
16. U.S. Food & Drug Administration. FDA updates and press announcements on NDMA in Zantac (ranitidine) – Update 2/10/2019. [online]. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-zantac-ranitidine
17. U.S. Food & Drug Administration. Statement on new testing results, including low levels of impurities in ranitidine drugs. Issued 1/11/2019. [online]. Available from: https://www.fda.gov/news-events/press-announcements/statement-new-testing-results-including-low-levels-impurities-ranitidine-drugs
18. Department of Health & Social care. Update - supply disruption alert. SDA/2019/005 (U2). Ranitidine: all formulations - supply disruption alert – second update. Issued 20/12/2019. [online] available from: https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=102952
19. Shepherd, GM. Hypersensitivity reactions to chemotherapeutic drugs. Clinical reviews in allergy and immunology. 2003. 24(3);253-62. [online]. Available from: https://pubmed.ncbi.nlm.nih.gov/12721396/
20. Boulanger, J. Boursiquot, J.N. et al. Management of hypersensitivity to platinum and taxane based chemotherapy: CEPO review and clinical recommendations. Current Oncology. 2014 21(4);630-641. [online]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4117628/
21. Boehm, D.K. Maksymiuk, A.W. Paclitaxel premedication regimens. Journal of the National Cancer Institute. 1996. 88(7); 463-5. [online]. Available from: https://pubmed.ncbi.nlm.nih.gov/8618242/
22. Kwon, JS. Laurie, E. et al. A comparison of two prophylactic regimens for hypersensitivity reactions to paclitaxel. Gynecologic Oncology. 2002. 84(3);420-25. [online]. Available from: https://pubmed.ncbi.nlm.nih.gov/11855881/
23. British Oncology Pharmacy Association (BOPA). Guidance on the use of H2 antagonists for the prevention and management of hypersensitivity. Version 1.0. Issued 3/6/2020. [online]. Available from: https://www.bopa.org.uk/resources/guidance-on-the-use-of-h2-antagonists-for-the-prevention-and-management-of-hypersensitivity/
24. Department of Health & Social care. A guide to managing medicines supply and shortages. Issued 11/2019. [online]. Available from: https://www.england.nhs.uk/wp-content/uploads/2019/11/a-guide-to-managing-medicines-supply-and-shortages-2.pdf
25. Markman M. Kennedy A. et al. Paclitaxel-associated hypersensitivity reactions: experience of the gynecologic oncology program of the Cleveland clinic cancer centre. Journal of clinical oncology. 2000. 18(1); 102-05. [online]. Available from: https://pubmed.ncbi.nlm.nih.gov/10623699/
26. Bentzen JD. Hansen HS. Phase II analysis of paclitaxel and capecitabine in the treatment of recurrent or disseminated squamous cell carcinoma of the head and neck region. Journal of the Sciences and Specialities of the Head and Neck. 2006. [online]. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/hed.20462
27. Quock J. Dea G. et al. Premedication strategy for weekly paclitaxel. Cancer Investigation. 2002. 5; 666-72. [online]. Available from: https://pubmed.ncbi.nlm.nih.gov/12197222/
28. Fedorowicz Z. Van Zureen EJ. et al. Histamine H2-receptor antagonists for urticaria. Cochrane Database Systemic Review. 2012. [online]. Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008596.pub2/full
29. Slichenmyer WJ. Donehower RC. et al. Pretreatment H2 receptor antagonists that differ in P450 modulation activity: comparative effects on paclitaxel clearance rates and neutropenia. Cancer Chemotherapy and Pharmacology. 1995. 36(3); 227-32. [online]. Available from: https://pubmed.ncbi.nlm.nih.gov/7781143/#:~:text=Abstract,reactions%20in%20patients%20receiving%20paclitaxel.
30. Greenberger PA. Patterson R. et al. Prophylaxis against repeated radiocontrast media reactions in 857 cases. Adverse experience with cimetidine and safety of beta-adrenergic antagonists. Archives of Internal Medicine. 1985. 145(12);2197-200. [online]. Available from: https://pubmed.ncbi.nlm.nih.gov/2866755/
31. Berger MJ. Dunlea LJ. et al. Feasibility of stopping paclitaxel premedication after two doses in patients not experiencing a previous infusion hypersensitivity reaction. Supportive Care in Cancer. 2012. 20; 1991-97. [online]. Available from: https://link.springer.com/article/10.1007%2Fs00520-011-1303-9
32. Berger MJ. Vargo C. et al. Stopping paclitaxel premedication after two doses in patients not experiencing a previous infusion hypersensitivity reaction. Supportive Care in Cancer. 2015. 23(7); 2019-24. [online]. Available from: https://link.springer.com/article/10.1007%2Fs00520-014-2556-x