British Oncology Pharmacy Association

bopa

Guidance on the use of H_2 antagonists for the prevention and management of hypersensitivity

To guide for members on the prevention and management of hypersensitivity in situations where H_2 antagonists are in short supply or unavailable

www.bopa.org.uk

Version 1.0
3rd June 2020

Contents

1. Scope 3
2. Introduction 3
3. Approach 3
4. Guidance 4
5. Table 1: H_2 Antagonists 6
6. References 7
7. Acknowledgements 8
8. Document control 8

1. Scope

1.1 This guidance has been developed to advise healthcare professionals on the prevention and management of hypersensitivity reactions to systemic anticancer therapy (SACT) in situations where H_2 antagonists are in short supply or unavailable.

2. Introduction

2.1 In Oct 2019 the Department of Health and Social Care (DHSC) issued a Supply Disruption Alert (SDA/2019/005) for ranitidine – all oral formulations, following an investigation of a contaminant, N-nitrosodimethylamine (NDMA), in samples of ranitidine active substance.[1] Following this, in Dec 2019 The Medicines and Healthcare products Regulatory Agency (MHRA) instructed suppliers to quarantine all affected, unreleased stock at manufacturer level. As of May 2020, ranitidine tablets, effervescent tablets, oral solution and injection are expected to be out of stock with no date for resupply. [2]

2.2 The DHSC has provided guidance on alternatives for patients prescribed ranitidine used within its license for gastrointestinal conditions. The DHSC guidance does not cover the commonly prescribed off-label use in the management of infusion reactions to SACT.

2.3 As many prescribers switch to alternative H_2 antagonists, the availability of these alternatives is also becoming unpredictable. In order to rationalize current stock of H_2 antagonists, this contingency guidance has been written to aid decision making in the prescribing of H_2 antagonists for the prevention and management of infusion reactions to SACT.

3. Approach

3.1 For many anticancer agents the evidence for the use of H_2 antagonists in the prevention and management of infusion reactions is variable and consensus in practice is inconsistent.[3,5,6]

3.2 As the availability of these agents becomes restricted it is important that guidelines and protocols are reviewed pro-actively, and the use of H_2 antagonists is rationalised to ensure these agents are reserved for areas of practice where there is evidence of need and effectiveness. In the areas where an H_2 antagonist is

clearly required, options for agents that could replace ranitidine should be agreed locally and documented in accordance with institutional policy.

4. Guidance

4.1 H_2 antagonists have been used off-label in in the prevention and management of infusion reactions to SACT in combination with other agents in three ways:

- Treatment of an infusion related reaction
- Standard pre-medication prior to some systemic anticancer therapies
- Additional pre-medication during re-challenge or as part of a desensitisation regime in patients that have previously reacted to a systemic anticancer therapy.[4]

4.2 **Review**

4.2.1 Remove routine use of H_2 antagonists from local treatment algorithms for the treatment of infusion-related reactions.

Rationale: Interpretation of evidence has been variable. Although ESMO Clinical Practice Guidelines[5] advocate use of H_1 & H_2 antagonists in the management of infusion related reactions, the Resuscitation Council (UK) states that there is little evidence to support the routine use of an H_2-antihistamine (e.g. ranitidine, cimetidine) for the initial treatment of anaphylactic reactions.[6] In the absence of ranitidine IV there is no available intravenous alternative, and the onset of action of most oral preparations is not suitable for the acute management of an infusion related reaction.

4.3 **Rationalise**

4.3.1 Routine use of H_2 antagonists as pre-medications for some systemic anticancer medicines may not be warranted.

Rationale: The evidence appraised for the ESMO Clinical Practice Guideline[5] summarises the use of prophylactic agents as pre-medications for some chemotherapy drugs. Use of H_2 antagonists is not indicated for many of the documented agents.

4.3.2 If patients receiving weekly paclitaxel experience no hypersensitivity reactions after the first two doses, remove pre-medication with dexamethasone, chlorphenamine and H_2 antagonist from dose 3 onwards (off-label).

Rationale: Although the product license states that patients on paclitaxel should have pre-medication with corticosteroids, antihistamines, and H_2 antagonists prior to every infusion to reduce the risk of hypersensitivity,[7] there has been research carried out into stopping premedication when there has been no reaction to the first two paclitaxel treatments.[8,9,10] This is already established practice at some cancer centres in the UK.

4.4 **Reserve**

4.4.1 Where supplies of ranitidine are available, these should be reserved for the following groups:

4.4.2 Paediatric population

Rationale: Alternative H_2 antagonists to ranitidine are limited in the paediatric population. Cimetidine is available as a liquid and may, in the absence of drug interactions, be given to children over 1 year of age.[11] Dosing information (unlicensed) is available for children and adolescents for oral famotidine and nizatidine. The use of these agents in smaller children is limited by the available dosage forms. Use of these agents should be approved for use in accordance with institutional practice.

4.4.3 Patients receiving paclitaxel and cabazitaxel (first two doses only for weekly paclitaxel)

Rationale: The SPCs for these agents require pre-medication with an H_2 antagonist as part of their product license(s).[6,12]

4.5 **Replace**

4.5.1 The choice of an appropriate an alternative will require consideration of multiple factors including timing of dose, evidence in specific indication, availability of product, interaction profile and patient suitability. A summary of alternatives to guide decision making is provided in table 1.

4.5.2 If no suitable alternative is available at all, then a clinical decision must be made between proceeding with treatment without an H_2 antagonist pre-med or switching to an alternative treatment which does not require an H_2 antagonist pre-med.

4.6 **Monitor**

4.6.1 The ranitidine shortage will necessitate a change in practice for healthcare providers, who may take a range of different approaches. It is important to monitor the effect that these changes have on reaction rates, to support decision making throughout the process and gather evidence to inform future practice.

4.6.2 Cancer pharmacists across the UK and the Republic of Ireland are invited to take part in a national service evaluation of paclitaxel infusion reactions, to be co-ordinated by BOPA.

5. Table 1: H_2 Antagonists

	Formulation	Timing of dose	Notable Interactions	Comments	Availability	Evidence
Ranitidine						
Strengths available: 150mg, 300mg (usual dose ADULT: 150mg – 300mg BD)[13]	Tablets	Peak plasma concentrations occur at 1 to 3 hours and bioavailability is relatively poor at approximately 50%[13]	Does not affect CYP450 enzymes (refer to SPC for interactions)	Unsuitable for acute treatment of IR. ADULTS: Consider 150mg PO prior to SACT regime.	Wide scale shortage	Paclitaxel SPC states 50mg IV for pre-medication. Cabazitaxel SPC states ranitidine Desensitisation: Use of 50mg IV 20 minutes prior to desensitisation regime.[4]
Cimetidine						
Strengths available: 200mg, 400mg and 800mg Liquid :200mg/5mL (usual dose ADULT: 400mg BD, max 2.4g /24hrs in divided doses)[11,14]	Oral preparations only (no licensed IV formulation available of cimetidine in the UK but oral doses are virtually completely absorbed.)	Peak levels occur after approx. 30mins **if taken on an empty stomach** (2 hours if taken after food).[15]	Cimetidine is a Weak CYP450 enzyme inhibitor (CYP1A2, 2C19, 2D6, and 3A457) that causes a > 1.25-fold but < 2-fold increase in the plasma AUC values or 20-50% decrease in clearance[16] (refer to SPC for full list of interactions)	Single stat doses used as a pre-medication for prophylaxis of hypersensitivity reactions are unlikely to have clinically significant interactions ($t_{1/2}$ = 2 hours). ADULTS: Consider 400mg PO 30mins before SACT regime	Widely available – however confirm stock levels due to increased demand, supply may be affected.	Paclitaxel SPC states 300mg IV for pre-medication.[7]
Famotidine						
Strengths available: 20mg and 40mg (usual dose ADULT: 20-40mg OD)[20]	Oral preparations only	Peak plasma concentrations are attained within 2- 4 hours; oral bioavailability ranges from 40 to 50%.[17] Not affected by food.	Does not affect CYP450 enzymes (refer to SPC for full interactions)	Unsuitable for acute treatment of IR. ADULTS: Consider use of 40mg PO, 4 hours prior to SACT regime.	Availability variable – not widely available. Confirm stock before switching.	Desensitisation: Use of 20mg IV 20 minutes prior to desensitisation regime.[4]
Nizatidine						
Strengths available: 150mg (usual dose ADULT: 150mg Od –BD, or 300mg OD)[18]	Oral preparations only	Peak levels occur at 30mins to 3hrs. Oral bioavailability is good (>70%) and not significantly influenced by food.[19]	Does not affect CYP450 enzymes (refer to SPC for full list of interactions)[18]	No known evidence of use in chemotherapy induced hypersensitivity prophylaxis or treatment.	Availability variable – least widely available. Confirm stock before switching.	No known evidence of use in chemotherapy induced hypersensitivity prophylaxis or treatment.

6. References

1. DHSC Supply Disruption alert SDA/2019/005 (available at www.cas.mhra.gov.uk – accessed 26/05/2020)
2. DHSC Ranitidine: all formulations – Supply Disruption Alert – second update alert SDA/2-19/005 (U2) (available at www.cas.mhra.gov.uk – accessed 01/06/2020)
3. Slimano, F, Coliat, P, Perotin, J *et al.* Is antihistaminergic H2 really useful in prevention of hypersensitivity induced by paclitaxel? *Support Care Cancer* 24: 4475–4477 (2016). https://doi.org/10.1007/s00520-016-3366-0
4. Mariana C. Castells, et al. Hypersensitivity reactions to chemotherapy: Outcomes and safety of rapid desensitization in 413 cases. *Food, drug, insect sting allergy, and anaphylaxis* 122 (3): 574-580 (2008) https://doi.org/10.1016/j.jaci.2008.02.044
5. S. Roselló et al. Management of infusion reactions to systemic anticancer therapy: ESMO Clinical Practice Guidelines. *Annals of Oncology*, 28 (suppl_4): iv100–iv118 (2017) https://doi.org/10.1093/annonc/mdx216
6. Resuscitation Council (UK) Emergency treatment of anaphylactic reactions: Guidelines for healthcare providers accessed: https://www.resus.org.uk/anaphylaxis/emergency-treatment-of-anaphylactic-reactions/ Jan 2020
7. SPC Paclitaxel 6 mg/ml concentrate for solution for infusion (last accessed via https://www.medicines.org.uk/emc on 7/1/20)
8. Yenilmez A et al. Paclitaxel pre-medication: A comparison of two steroid pre-medication protocols. *J Oncol Pharm Pract*. 2016. ePub.
9. Berger MJ et al. Feasibility of stopping paclitaxel premedication after two doses in patients not experiencing a previous infusion hypersensitivity reaction. *Support Cancer Care* 20: 1991-7 (2012)
10. Berger MJ et al. Stopping paclitaxel premedication after two doses in patients not experiencing a previous infusion hypersensitivity reaction. Support Care Cancer. 2015. 23(7): 2019-2024, https://doi.org/10.1007/s00520-014-2556-x
11. SPC Cimetidine 200mg/5ml Oral Solution (last accessed via https://www.medicines.org.uk/emc on 1/6/20)
12. SPC Cabazitaxel: JEVTANA 60 mg concentrate and solvent for solution for infusion. (last accessed via https://www.medicines.org.uk/emc on 1/6/20)
13. SPC Zantac 150mg tablets (last accessed via https://www.medicines.org.uk/emc on 25/10/19)
14. SPC cimetidine 400mg tablets (last accessed via https://www.medicines.org.uk/emc on 25/10/19)
15. A. GrahnénC, von BahrB, LindströmA, Rosén. Bioavailability and pharmacokinetics of cimetidine. *European Journal of Clinical Pharmacology* 16 (5): 335–340 (1979)
16. Indiana University, Drug Interactions Flockhart Table ™ https://drug-interactions.medicine.iu.edu/MainTable.aspx (last accessed 25/10/19)
17. Echizen H1, Ishizaki T. Clinical pharmacokinetics of famotidine. *Clin Pharmacokinet* 21(3):178-94 (1991)
18. SPC Nizatadine 150mg capsules (last accessed via https://www.medicines.org.uk/emc on 25/10/19)

19. Nizatidine - FDA https://www.accessdata.fda.gov › drugsatfda_docs › label (last accessed 25/10/19)
20. SPC famotidine 20mg tablets TEVA: http://products.tevauk.com/mediafile/id/46378.pdf (last accessed 1/6/20)

7. Acknowledgements

7.1 The authors would like to thank everyone who contributed to this document.

8. Document control

Title	BOPA: Guidance on the use of H_2 antagonists for the prevention and management of hypersensitivity, version 1.0
Authors / Editors version 1.0	Lead author: Fleur Harvey, Lead Haemato-oncology Pharmacist, The Royal Marsden NHS Foundation Trust With input and advice from: Zaida Sheriffdeen, Lead Ambulatory Care Pharmacist, The Royal Marsden NHS Foundation Trust Emma Foreman, Consultant Pharmacist, The Royal Marsden NHS Foundation Trust Lucia Van Bruggen, Lead Pharmacist for Children and Young People, The Royal Marsden NHS Foundation Trust Gurpal Grewal, Joint Formulary & Medicines Optimisation Pharmacist, North Central London Calum Polwart, Specialist Oncology Pharmacist, South Tees NHS Foundation Trust Kristen Moorhouse, Lead Pharmacist for oncology, Oxford University Hospitals NHS Trust Seonaid MacLachlan, Principal Pharmacist, Cancer Services, NHS Ayrshire and Arran Catherine Loughran, Cancer Pharmacist, Nottingham University Hospitals & NHS England and NHS improvement, Midlands
Owner	BOPA.

Change History

Draft	Date	Lead Author/Editor	Summary of Change

Proposed Target Audience	All BOPA Members
Proposed Circulation List	BOPA Members, Chief pharmacists, Oncologists and haematologists
Contact details	contact@bopa.org.uk