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MARKET WITHDRAWAL OF INTRAVENOUS RANITIDINE

In October 2019, the Spanish Medicines and Healthcare Products Agency (AEMPS) announced a precautionary recall of all the batches of ranitidine in Tablet form available in the market as a result of the presence of N-nitrosodimethylamine (NDMA) impurities in some of the batches evaluated as part of an analysis performed by the European Medicines Agency.1

In November 2020, the EMA announced the suspension of the market authorization of ranitidine for all EU member states and established a grace period that expired on 25 November 2021. As the manufacturer did not take the steps required to revoke the suspension, the AEMPS decided to revoke the authorization of all ranitidine-based formulations marketed in Spain intended for parenteral administration.2

As ranitidine was the only intravenous receptor antagonist (H2RAs) available in Spain, medicines containing intravenous ranitidine were considered essential for some therapeutic indications such as the prevention of hypersensitivity and reactions to the infusion of taxanes (paclitaxel and cabazitaxel) and patisiran. That is the reason why a grace period was allowed in Spain.

With the marketing of IV ranitidine definitively suspended in Spain, the AEMPS is currently making arrangements for the drug famotidine (2 ml) 10 mg/ml injectable suspension to be imported into the country. This medicine will be made available under the Exceptional Circumstances Authorization hanism for the prevention of hypersensitivity reactions to the infusion of taxanes and patisiran.

For all other cases, the Spanish market has drugs containing other active ingredients. These include proton pump inhibitors (omeprazole, pantoprazole, lansoprazole, esomeprazole) and other orally-administered H2RAs such as famotidine.

THERAPEUTIC ALTERNATIVES FOR CANCER PATIENTS

Following its review of the use of IV H2RAs in patients treated with taxanes such as paclitaxel, SEFH's Oncology Pharmacy Workgroup (GEDEFO) wishes to point out the following:

Obligatory use of intravenous H2RAs

Several studies claim that anti H2 need not always be used as pre-medication in the prevention of hypersensitivity reactions associated with administration of paclitaxel.

A prospective pre-post intervention study on 183 treated with paclitaxel published in the British Journal of Cancer compared a standard pre-medication regimen (corticosteroids with an H1RA) combined with ranitidine with the same standard regimen without ranitidine, demonstrating that the incidence of grade ≥3 hypersensitivity reactions was non-inferior in the group not receiving ranitidine (1.6%) than in the group receiving ranitidine (4,4%) (difference: −2,7%, 90% CI: −6,2% to 0,1%).

As regards reactions of any grade, their incidence in patients without ranitidine was non-inferior (12%) than in those with ranitidine (20%) (difference: −8,2%, 95% CI: −15,0% a −1,4%, p = 0,046).3 In another article in the same issue of the same journal, Gelderblom et al4 published an editorial where they dwelled on the weakness of the evidence supporting the use of H2RAs to prevent hypersensitivity reactions and claim that their use should be avoided in that context.

In another study on 449 patients with breast cancer, pre-medication was administered during the first two cycles of paclitaxel and discontinued if no hypersensitivity reactions occurred. This study showed that 0.85% of patients where the pre-medication was withdrawn required salvage treatment due to the appearance of hypersensitivity reactions.5

Unfortunately, no similar studies exist for cabazitaxel However, the rationale for the use of H2RAs is the same, although the risk of infusional reactions is lower as cabazitaxel, unlike paclitaxel, is not formulated with cremophor but with polysorbate 80, whose SmPC does not contemplate the use of H2RAs.

The use of oral H2RAs

The pre-medication to prevent infusional reactions may be administered orally, ideally at least 30-60 minutes before the patient takes their H2RA dose. In this context, oral administration of famotidine6 may be considered, in cases where a H2RA is indicated.

A recent phase II clinical trial on cabazitaxel used all H2RAs, except for cimetidine, as pre-medication. The drug's SmPC recommends the use of ranitidine or an equivalent drug. According to Cancer Care Ontario's Management of Cancer Medication-Related Infusion Reactions guidelines, H2RAs may be administered either orally or intravenously.7

It should be added that, according to a recent search on the Murcia Region's Preevid system, the use of H2RAs in case of anaphylaxis is not well-supported in the literature and should be avoided.8,9

For all the reasons above, we consider that the AEMPS notice expressly stating that intravenous pre-medication with H2RAs is indispensable to reduce the risk of infusional reactions should be revised. We believe it would be best to indicate that the use of H2RAs has been the norm in patients with hypersensitivity reactions without saying that administration of such drugs should be obligatory, thereby facilitating the clinical use of H2RA-free orally-administered alternatives.

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