Ranitidine in short supply: Why now, and where next?

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Word Count: 1086

Keywords: Ranitidine, Pharmacology, Pharmacy, Deprescribing

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Ranitidine is currently in very short supply, both in the UK, and around the world. Major manufacturers have undertaken a product recall, and new stock is not being released to the market. Despite the sudden shortage of Ranitidine occurring from mid-October, shortly before the previous BREXIT deadline, this situation is not related to the UK’s relationship with the EU. Rather, this situation has arisen because of concerns over potentially carcinogenic impurities within the medication, and affects most brands from most manufacturers.

The issues began after a review by the European Medicines Agency (EMA) identified that some ranitidine brands were found to contain low levels of the nitrosamine impurity called N-nitrosodimethylamine (NDMA). NDMA is classified as a probable human carcinogen by the International Agency for Research on Cancer (IARC), the specialised cancer agency of the World Health Organisation (WHO). However, it is also accepted that NDMA can be an environmental contaminant found in water supplies and food (dairy products, meat and vegetables). A similar situation arose in 2018, with investigations into NDMA and other nitrosamine impurities potential presence in angiotensin II receptor blockers (ARBs). This also resulted in the recommendation for numerous recalls due to unacceptable levels of nitrosamines, but was not a significant issue in paediatric practice due to the low level of use of ARBs. With regards to ranitidine, neither the EMA nor the Medicines and Healthcare Products Regulatory Agency (MHRA) have indicated that there is a current risk to patients although we are aware that an EMA safety review has been commenced. It therefore has not been withdrawn and can still be prescribed. However, pharmacies are having great difficulty in obtaining stock as several manufacturers of ranitidine products including TEVA [1], Perrigo [2], and GSK (manufacturer of the originator product Zantac®) [3] have recalled their products. It is this disruption in the supply chain that is leading to the shortages.

Ranitidine’s mechanism of action is via competitive antagonism of the Histamine-2 (H2) receptor. As well as directly reducing acid production from parietal cells, the inhibition of the H2 receptors in the stomach reduces the output of pepsin, further reducing the volume of gastric acid secreted. Although it has a half-life of only 2-3 hours, the duration of action in adults is considerably longer, suppressing acid secretion from gastric parietal cells for approximately 12 hours. It is important to note that ranitidine does not reduce the frequency of any reflux events, but reduces the associated symptoms. Ranitidine is well tolerated, has low incidence side effects, and is available in a palatable liquid formulation that aids administration to babies and infants. All of this contributes to the common practice of using ranitidine to treat GORD in infants and children. However, there is sparse data supporting its efficacy, especially in infants [4], and in the medium term, further studies into the efficacy of ranitidine in the management of GORD in children are needed[4].

There are potential difficulties from use of ranitidine. Long term use is limited by tachyphylaxis (acute decrease in response to a drug post administration), which can develop within 14 days[4, 5]. In addition, while the incidence of ranitidine related adverse effects is low, constipation, diarrhoea, dizziness and fatigue are all recognised[4]. Ranitidine is also believed to increase the risk of community acquired pneumonia and gastro enteric infection, predominantly *Clostridium difficile* [5].

For paediatricians, the issue will relate to how to manage their patients who are already using it. The current advice from the Royal College of Paediatrics and Child Health is to ‘be aware of these withdrawals and consider de-prescribing or switching after a medication review’. Clearly, there is no “one size fits all” approach that will work here, and individual patient circumstances will need to be taken into account. These could include: The level of symptoms previously experienced; current level of symptoms; natural history of the underlying condition (e.g. improvement after weaning expected in infantile GORD); current level of symptomatic relief believed to be attributed to ranitidine; age of the patient; presence of feeding tubes; renal disease and/or osteoporosis.

If there are no current symptoms, then unless there are other extenuating circumstances (e.g. previous GI bleeds, or failure to thrive, related to severe GORD), then it would seem reasonable to attempt to stop the medicine. This would need to be planned, and supervised, to ensure that if patients are experiencing recurrence of symptoms then access to healthcare staff who can provide alternate medications is possible.

If de-prescribing is not achievable, then there are only a couple of options to consider with regard to alternate medications. If the patient is not already using a simple antacid such as Alginic Acid, and is not constipated (or predisposed to constipation), then this may be a suitable alternative. This preparation works by increasing the viscosity of the gastric contents, leading to thickened feed (aiming to reduce reflux events) and neutralise gastric acid (symptomatic relief).

Finally, if the patient is not using a proton pump inhibitor (PPIs), then these can be considered. PPIs work through irreversibly inactivating the parietal cell membrane transporter H+/K+-ATPase, resulting in decreased acidity of gastric acid and total volume of gastric secretions, aiding gastric emptying [4]. Omeprazole is licensed for children in the UK over the age of 1 year. With regards to acid suppression omeprazole is more potent than ranitidine, but the formulation is harder to administer to infants when used off-label in this age group. Omeprazole is a once daily dosing regime, which would be expected to be beneficial in terms of adherence, however the anecdotal responses from parents in clinic suggests that the difficulties in administration in young babies in particular (dislike of taste and/or texture). In addition, the liquid formulation of omeprazole remains unlicensed, and administration of the other formulations via feeding tubes can be difficult. So despite the fact that rantidine is dosed two or three times a day, these factors may help explain why it has retained its popularity in paediatrics, when adult medicine has migrated more towards PPIs. Omeprazole, like the H2 receptor antagonists, is largely well tolerated but does have adverse effects to consider, including hypomagnesaemia, nephrocalcinosis, and erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), anaphylactic shock and hepatic failure.

Given the current situation regarding ranitidine and its future availability as a prescribable medicine, paediatricians should prepare and understand what options are currently available as alternatives for their patients. The choice to either de-prescribe or switch to an alternative therapeutic option should be a case-based decision and reflect the concerns from the patients and families.

Word Count: 1086

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