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CASE REPORT

Can H_2-receptor upregulation and raised histamine explain an anaphylactoid reaction on cessation of ranitidine in a 19-year-old female? A case report

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The anaphylactoid reaction described follows cessation of ranitidine in a 19-year-old female with the disease cluster: mast cell activation syndrome, hypermobile Ehlers-Danlos syndrome and postural tachycardia syndrome. Anaphylaxis can give wide-ranging symptoms from rhinorrhoea and urticaria to tachycardia and system-wide, life-threatening, anaphylactic shock. Individuals with a disorder of mast cell activation can experience many such symptoms. H_2 receptor antagonists, such as ranitidine, are commonly prescribed in this population. A mechanism for the reaction is proposed in the context of ranitidine, as an inverse agonist, causing upregulation of H_2 histamine receptors and raised histamine levels due to enzyme induction. This effect, following extended and/or high antihistamine dosing, may have implications for other individuals with a disorder of mast cell activation, such as mastocytosis or mast cell activation syndrome. There are potential policy and patient guidance implications for primary and secondary care with respect to cessation of H_2 antagonists.

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Introduction

Anaphylaxis, a type 1 hypersensitivity response, can be a life-threatening event caused by flooding of mast and basophil cell-derived mediators in response to a stimulus. Drug-induced anaphylaxis has increased in frequency with the advent and administration of a widening array of therapeutic agents. **Ranitidine**, an **H_2 receptor** antagonist, is one such medication which has been reported, albeit rarely, to cause anaphylaxis upon initiation [1]. Although hyperacidity following cessation of ranitidine has been well-documented, to the best of our knowledge, wider histaminergic symptoms have not.

The first effective, orally active and non-toxic H2 antagonist, cimetidine, was marketed in 1976. Ranitidine followed in 1981 and with benefits of increased potency and compatibility with other drugs, lacking the enzyme P450 inhibiting effects of cimetidine, it became a first choice to reduce gastric acid output in gastro-oesophageal reflux disease, functional dyspepsia and benign gastric or duodenal ulceration [2]. Although its use has been to a large extent superseded by proton pump inhibitors (PPI), such as lansoprazole and omeprazole, it is still widely prescribed and is also available to purchase in lower strength formulations from UK pharmacies and other retail outlets. Individuals with hypermobile Ehlers-Danlos syndrome and/or a disorder of mast cell activation can be prescribed ranitidine to manage gastric symptoms.

The *Ehlers-Danlos syndromes* (EDS) are rare heritable disorders of connective tissues. These syndromes have until recently been classified under the Villefranche Nosology, which described six subtypes of the disorder. In March 2017, the International EDS Consortium proposed a revised classification of thirteen EDS subtypes [3]. Hypermobile EDS (hEDS) is the most common of these subtypes with a prevalence of 1–5 per 10 000 individuals. hEDS is diagnosed by satisfying clinical criteria relating to generalized joint hypermobility, family history and the presence or absence of signs and symptoms of other connective tissue disorders [3]. Functional gastrointestinal problems are common, and individuals can suffer gastric reflux, nausea, abdominal discomfort and altered gut transit times, leading to both constipation and diarrhoea [4, 5].

Disorders associated with *mast cell activation* include mastocytosis and the poorly understood mast cell activation syndrome (MCAS, or idiopathic MCAS). Current proposed MCAS diagnostic criteria are episodic multisystem symptoms consistent with mast cell activation (which can be due to both IgE- and non-IgE-mediated triggers); appropriate response to medication that targets mast cell activation; documented increases in validated systemic markers of mast cell activation during a symptomatic period compared with the patient's baseline values [6]. However, mast cell activation that is associated with another chronic inflammatory disease does not always meet the diagnostic criteria and can be difficult to diagnose [7, 8]. In these patients, there is commonly a history of multisystem morbidity of an inflammatory or allergic nature and features of inappropriate mast cell activation, but without evidence of mast cell proliferation [9]. It has further been proposed that lack of raised tryptase, where there is evidence of elevated **histamine**, suggests involvement of basophils and that gastric signs and symptoms appear to be more associated with raised histamine than tryptase [10, 11]. An association between hEDS, MCAS and postural tachycardia syndrome (PoTS) has been identified [12].

The biogenic amine histamine is synthesized and stored in 'professional' basophils and mast cells and released through exocytosis to play a central role in inflammatory or allergic reactions. Four histamine receptor subtypes have been identified, H_1, H_2, H_3 and H_4; all are G protein-coupled receptors (GPCRs) [13]. Constitutive or spontaneous activity, where a receptor response can be generated in the absence of bound agonist, has been shown for many GPCRs including histamine receptors [12, 14]. According to the two-state model for GPCR function, receptors can switch between resting and activated states. Where constitutive activity occurs, a proportion of receptors exists in the active conformation in the absence of bound ligand. Agonists tend to shift the equilibrium towards the active receptor state, while inverse agonists shift it towards the resting state [15, 16]. The H_2 receptor ligand ranitidine is known to act as an inverse agonist at the H_2 histamine receptor [17].

Histamine is arguably the most pleiotropic chemical in the human body, and its receptors have a wide distribution. H_1 receptors are located in the central nervous system (CNS), smooth muscle, sensory nerves, heart, immune and skin cells, among others [13]. Stimulation of these receptors can give rise to symptoms due to bronchiolar and gastrointestinal (GI) smooth muscle contraction (causing bronchospasm and difficulty breathing, and diarrhoea, respectively); sensory stimulation of the epidermis and dermis (causing itch and pain); vasodilation (causing hypotension, flushing and headache) [16].

H_2 receptors are also widely distributed and found in high concentrations in gastric mucosa, the uterus, CNS, heart and vasculature, respiratory tract and cells involved in immune function [13, 16]. The majority of histamine receptors in the skin are thought to be H_1, with around 15% being H_2 [18]. Stimulation of H_2 receptors promotes hydrochloric acid secretion from gastric parietal cells and can cause symptoms associated with gastric hyperacidity. H_2 receptor stimulation in the cardiovascular system increases heart rate and contractility.

H_3 receptors are highly expressed in the CNS and have a wide distribution elsewhere in the body, including the GI tract, heart, skeletal muscle and sensory nervous system, including in the dermis [13]. Less is known about the most recently discovered H_4 histamine receptor, although mRNA expression studies have indicated a wide distribution and particular abundance in cells of the immune system, including lymphocytes, monocytes, neutrophils and eosinophils. H_4 expression has also been demonstrated in the sensory nervous system, skin fibroblasts, GI tract and kidney [13]. Definitive demonstrations of protein and functional expression have, however, yet to be reported [13].

The potentially life-threatening symptoms associated with anaphylaxis are multifaceted and include hypotension, bronchospasm, gastrointestinal symptoms, angio- and laryngeal oedema, cutaneous symptoms and hypothermia [19, 20]. These symptoms are induced in susceptible individuals by diverse triggers, including certain foods, insect stings, stress and medication. Such triggers bring about release of the mediators of the pathophysiological effects seen in this serious allergic

reaction in which histamine has a central role acting at its receptors located on the affected cells/organs. There is also evidence that histamine influences the activity of a number of inflammatory cell types and is implicated in allergic inflammation via all of the histamine receptors [21], with H_3 and H_4 displaying notable high potency for histamine [13].

Case report

Here, we report anaphylactoid symptoms in a white British female aged 19 with co-morbidities of hEDS, MCAS and PoTS, which followed cessation of high-dose ranitidine and culminated in administration of adrenaline.

Medication in the days preceding the anaphylactoid event were cetirizine tablets 10 mg, one at night; Slow Sodium tablets 600 mg, 8 daily; paracetamol tablets 500 mg, one or two when required, (not taken in the week prior to the event); ondansetron tablets 4 mg, one when required (not taken in the week prior to the event); omeprazole tablets 10 mg (not taken in the week prior to the event), two at night; and ranitidine 300 mg tablets, one twice daily (dose increased from 300 mg to 600 mg daily, 5 weeks prior to the event).

The patient had been advised to stop gastric acid-altering medication in readiness for a gastroscopy and had gradually reduced the dose of omeprazole over a 1 week period; dosing had stopped 10 days prior to the anaphylactoid event. In the 3 days preceding the event, ranitidine was reduced as follows: day 1 – morning dose was omitted and 300 mg was taken in the evening; day 2 – morning dose was taken and further dosing stopped. The patient became symptomatic from the evening of day 3 onwards, with symptoms worsening from the morning of day 4.

The patient had not experienced anaphylaxis before; the only IgE-mediated allergy she had shown previously was to latex. She had identified a number of food intolerances which caused gastric symptoms, but these symptoms had improved following the addition of H_1 (cetirizine) and increased H_2 (ranitidine) antihistamine medication. She was following a low-FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) diet [22] and low histamine diet and had not eaten anything different to normal in the days leading up to the event.

Symptoms leading to administration of adrenaline

On day 3 (described above), the patient experienced abdominal cramps and shivering in the evening and felt cold and dizzy. She woke through the night due to abdominal pain and felt shivery and cold and generally unwell. The abdominal pain continued the following morning, and she described feeling shivery, having a running nose and a tight throat, and finding her breakfast hard to swallow. She described looking at her tongue in the mirror because it felt 'weird'. She had not experienced these symptoms before. Despite symptoms, she went to college but continued to feel cold and noticed a mild red blotchy rash on her arms and felt somewhat itchy all over. Her throat became more bothersome and her chest started to feel tight; at this point, she sought medical attention.

At the minor injuries unit, she was seen immediately. On arrival at 11:07, she was given a 4 mg stat dose of oral H_1 antagonist, chlorphenamine. Recorded observations at 11:15 were temperature 36.6°C; pulse 96 beats/min; respiration rate 15 breaths/min; blood pressure 140/87 mmHg; oxygen saturation 99.8%. At 11:35, observations were pulse 83 beats/min; respiration rate 20 breaths/min; blood pressure 143/79 mmHg; oxygen saturation 100%. No flushing, urticaria, stridor or angioedema were observed. At 11:45, the tightness in her chest and throat increased, face flushed, oxygen saturation dropped to 92% and she was administered a stat dose of adrenaline (0.5 ml, 1:1000) and oxygen was commenced. Symptoms rapidly abated, and she was transferred to the general hospital for observation. She recovered quickly and fully.

Discussion

The case report describes the symptoms experienced by a 19-year-old female following cessation of the H_2 receptor antagonist ranitidine. The patient had been prescribed ranitidine to manage gastric symptoms associated with mast cell activation and had taken a 600 mg daily dose for 5 weeks prior to the event described here, which coincided with withdrawal of the drug. The 600 mg daily dose is at the licensed maximum and is consistent with recommended dosing for prophylaxis and healing of NSAID (non-steroidal anti-inflammatory drugs)-induced duodenal and gastric ulcers, and moderate to severe GORD (gastro-oesophageal reflux disease) [23]. A dose of 300 mg daily is, however, more commonly seen in practice.

The early symptoms of shivering, stomach cramps, giddiness (or dizziness, as described by the patient), rhinorrhoea and tongue and throat symptoms experienced by the patient are classic symptoms mediated by histamine, acting at its widely distributed G protein-coupled receptors.

H_1 and H_2 receptors are co-expressed by many cell types at varying densities, whilst H_3 and H_4 receptors appear to have a more limited distribution [13]. Stimulation of H_1, H_2 and H_3 receptors has been implicated in inducing hypothermia in rodents [20, 24, 25], and abdominal pain and diarrhoea in humans [25]. The patient's subsequent symptoms of chest and throat tightness and flushing are also those of registered anaphylactic reactions attributed to H_1 and H_2 receptor stimulation [26]; a contribution from activated H_3 and H_4 receptors cannot be discounted.

Fullarton and colleagues [27, 28] reported the well-documented rebound nocturnal hyperacidity after abrupt withdrawal of a number of H_2 receptor antagonists, including ranitidine. The authors proposed that the underlying mechanism responsible for this phenomenon could be upregulation of parietal cell H_2 receptors. Since then, the concept of constitutive, or spontaneous, activity of many GPCRs has developed, including histamine receptors, in which a proportion of receptors exist in an active state in the absence of agonist [14]. Although almost all of these studies have been conducted in genetically manipulated systems (reviewed in [13]), it is important to note that spontaneous activity of H_3

receptors has been recorded in a native system [29]. It seems likely that the related H_2 receptor also exhibits this behaviour *in vivo*.

In 1996, using a transfected cell model, Smit *et al*. demonstrated that a number of H_2 receptor antagonists, including ranitidine and cimetidine, acted as inverse agonists driving the receptor equilibrium towards the resting state. In doing so, these ligands inhibit basal, agonist-independent, activity [17]. The authors described an increase in H_2 receptor density following exposure to ranitidine and cimetidine that was both time- and dose-dependent. This upregulation led to increased basal ligand-independent activity which they suggested might underlie tolerance to these drugs and also contribute to the rebound hyperacidity experienced by patients. Jones *et al*. [30] observed an exaggerated response to a histamine analogue in patients who had been treated for 3 months with ranitidine at a dose of 150 mg at night. They suggested that this observation reflected an increase in receptor number (or upregulation). Upregulation is believed to relate to suppression of H_2 receptor degradation and the recycling of H_2 receptors [31].

Symptoms of rebound hyperacidity have been observed in patients between 24 and 48 h after the final dose of H_2 antagonist [28, 32]. This is consistent with the appearance of the histaminergic symptoms in the case reported here, which began to develop 36 h from the last dose of ranitidine and became severe at 48 h. It is tempting to speculate that, in this case, chronic treatment with high-dose ranitidine led to H_2 receptor upregulation, giving rise to an increased population of spontaneously active receptors and resulting in H_2 receptor-mediated histaminergic symptoms.

It should be noted that the patient involved in this report had been diagnosed with MCAS, where symptoms are experienced as a result of excessive release of pro-inflammatory mediators, including histamine. In such a case, the consequences of ranitidine-induced receptor upregulation could conceivably be magnified, leading to extreme symptoms upon abrupt cessation of ranitidine dosing.

An upregulation of H_2 receptors might reasonably account for those symptoms that are obviously mediated by this class of receptor, such as abdominal discomfort. It is less clear how it could account for effects mediated by H_1 (or H_3 or H_4) receptors. It has recently become apparent, however, that crosstalk exists between co-localized H_1 and H_2 receptors, with heterodimers forming and being co-internalized when either receptor is stimulated [33, 34]. Once internalized, these receptor dimers may contribute to signalling events and to the overall cellular response. If such events prove to be commonplace, this crosstalk between H_1 and H_2 receptors could explain the appearance of H_1-mediated symptoms, such as rhinorrhoea, that were experienced by this patient.

Histamine is synthesized from histidine in a reaction catalysed by histidine decarboxylase (HDC). Monczor and Fernandez [33] described induction of this enzyme by the H_2 receptor antagonist famotidine, resulting in increased levels of histamine, which the authors suggested could contribute to rebound hyperacidity [33]. Such an increase in histamine may be expected to evoke cellular effects mediated by all histamine receptors, and conceivably to an exaggerated response through the upregulated population of H_2 receptors following antagonist exposure, as seen in this patient.

Animal studies have shown that the turnover of histamine varies in different tissues, with resultant differences in histamine half-life (t½) of minutes to several days [35]. This variation in histamine turnover has a number of possible explanations in addition to alterations in local tissue HDC. These include receptor-mediated changes in histamine metabolizing enzymes (histamine N-methyl transferase, diamine oxidase), enzyme polymorphisms [36] and differences in histamine uptake activities (deranged histamine turnover). It has also been known for many years that in certain tissues, such as gastric mucosa, H_2 receptor antagonists modulate histamine breakdown by histamine N-methyltransferase [37]. Differences in turnover of histamine in the various tissues affected could account for the timing of symptom onset experienced by the patient.

Taken together, these findings offer a plausible explanation for the symptoms experienced by the patient, which were apparently precipitated by withdrawal of the H_2 receptor antagonist ranitidine. It is proposed that upregulation of H_2 receptors and/or increased levels of histamine underlie these effects. Through crosstalk between H_1 and H_2 receptors, activation of H_1 receptors might also contribute to the full gamut of symptoms experienced by the patient. It is postulated that the severity of symptoms here was a consequence of the sustained duration of high-dose ranitidine, followed by its rapid removal, and the patient's disorder of mast cell activation and hEDS.

Patients with a disorder of mast cell activation (and also gastric symptoms associated with hEDS) can be prescribed both H_1 and H_2 antagonists at elevated doses that are above the manufacturer's guidelines for the drug. This patient was prescribed ranitidine at the maximum dosage and cetirizine at the normal recommended dose. If this reaction had been predicted, increasing the dose of H_1 antagonist prior to ranitidine withdrawal might have reduced the adverse symptoms associated with cessation.

Although hypotension is common in anaphylaxis, patients can also display hypertension which may be a stress response [38]. In the half hour leading up to the administration of adrenaline, two raised systolic readings were recorded in this patient. The effect of anxiety on blood pressure and in promoting further mediator release, thereby exacerbating symptoms in the hospital, cannot be ruled out. In addition, antagonizing H_2 receptors has been reported to modify the turnover of 5-hydroxytryptamine (5-HT) [39], another mediator of anaphylaxis and modulator of mood. Mast cell 5-HT, together with histamine released following intestinal anaphylaxis, can stimulate mesenteric afferents via 5-HT_3 and histamine H_1 (not H_2 or H_3) receptors. Information regarding intestinal immune status can therefore be rapidly relayed to the CNS and may play a critical role in neural reflexes and behavioural responses [40, 41].

Conclusions and possible implications for therapy and policy

The prescribed dose of ranitidine was the maximum recommended daily dose for the drug. Patients referred for gastroscopy are advised to stop taking medications that interfere with

gastric acid production; this includes proton pump inhibitors and H_2 receptor antagonists. Advice varies as to when medication should be interrupted and usually recommends cessation 1 or 2 weeks before the procedure. There is no recommendation to taper the dose of H_2 antagonists leading to stoppage.

Gradual reduction in dose, leading to stoppage, may or may not have been sufficient to avoid or reduce symptoms associated with excess histamine, or enhanced histamine sensitivity, in this patient. As described above, rebound hyperacidity following abrupt cessation of H_2 antagonists is well-documented. Outstanding questions relate to whether the reaction reported here occurred as a consequence of the prior high dose and duration of ranitidine treatment; the abruptness of cessation; the patient's disorder of mast cell activation (and hEDS); or a combination of some or all of these factors. It is proposed that further investigation of widespread histaminergic symptoms in relation to cessation of H_2 antagonists may be of benefit, and in particular amongst this population who may be at increased risk.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [42], and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 [43].

Competing Interests

There are no competing interests to declare. S.A. is a relative of the patient.

The patient was treated at the Minor Injuries Unit, Townlands Memorial Hospital, Henley, Oxon RG9 2DR and transferred for observation to Royal Berkshire Hospital, Reading, Berks RG1 5AN.

This is a retrospective case report of an unpredicted adverse event following drug withdrawal. Informed written consent to obtain hospital results and to publish was obtained from the patient. Patient identity is protected and confidentiality observed at every stage.

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