

EDITORIAL

Clinical & Experimental Allergy

Does gastric acid suppression increase the risk of drug allergies?

This editorial discusses the findings of the paper in this issue by Riemer et al. [7].

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Adverse drug reactions (ADR) are a major clinical problem, with one study suggesting that over a 30-year period, even after excluding prescribing errors, ADR represented the fourth leading cause of death in hospitalized patients in the United States, exceeded only by heart disease, stroke and cancer [1]. In two UK hospitals, 6.5% of admissions were judged to be definitely, probably or possibly related to an ADR, with 2.3% of these ADR proving fatal [2].

In approximately 20–25% of ADR, non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin are implicated [3], reflecting at least in part the widespread use of these drugs both as prescription medications and as OTC analgesics. NSAIDs are a chemically diverse group of drugs that share the ability to inhibit the generation of prostanoids involved in inflammation and hyperalgesia. Type A ADR are typically related to dose and duration of treatment and may occur in a significant proportion of the patient population [4]. Type A reactions to NSAIDs are causally related to their inhibition of cytoprotective prostanoids involved in maintaining the gastric mucosal barrier, renal blood flow and haemostasis.

Many NSAIDs, however, also elicit Type B (hypersensitivity) reactions, in which sub-therapeutic doses or isolated exposures can cause acute bronchoconstriction, rhinoconjunctival symptoms, urticaria, angioedema or anaphylaxis in small sub-populations of susceptible individuals [5]. In the majority of such cases, patients show cross-sensitivity to NSAIDs that share different chemical structures, may experience reactions on first exposure, and typically do not show positive RAST or skin tests to the precipitating drug or drugs. These pseudoallergic reactions include aspirin-exacerbated respiratory disease

(AERD) in which inhibition of cyclooxygenase-1 by an NSAID [6] triggers the release over 1–2 h of potent bronchoconstrictor and vasoactive mediators, particularly cysteinyl leukotrienes, leading to an acute exacerbation of pre-existing asthma and/or allergic rhinitis. The trigger mechanism underlying AERD remains unclear, but may involve the shunting of arachidonic acid, the common precursor of the prostanoid and leukotriene families of lipid mediators, from the former pathway to the latter. Alternatively, leukotriene synthesis may be normally suppressed by a COX-1 product, probably PGE₂, and the removal of the PGE₂ by NSAIDs liberates the leukotriene response. In either case, NSAIDs are usually to be avoided by asthmatics as susceptible individuals are not easily identifiable; inadvertent ingestion of an NSAID is implicated in a significant proportion of cases of acute severe asthma exacerbation requiring ventilation in intensive care units [5].

In this issue of *Clinical & Experimental Allergy*, a team at the University of Vienna led by Dr Erika Jensen-Jarolim report on a much rarer form of NSAID hypersensitivity apparently involving a true allergic (IgE-mediated) reaction to oral diclofenac, an NSAID of the acetic acid class and raise the intriguing possibility that such reactions may be enhanced in patients in whom gastric acid secretion is suppressed by concomitant use of a protein pump inhibitor (PPI) such as omeprazole [7]. They describe an otherwise healthy male patient with no prior history of allergy or urticaria who experienced generalized urticaria within 1 h of ingesting diclofenac; he had one previous exposure to the drug, demonstrated diclofenac-specific IgE and did not react adversely to a chemically unrelated NSAID (aspirin), but he had been taking omeprazole for recurrent reflux oesophagitis concomitantly with the diclofenac. Urticarial reactions to a single NSAID have been reported in < 1% of healthy subjects without pre-existing urticaria [5]. Based on previous work showing that gastric acid suppression by PPI drugs can enhance IgE sensitization and promote allergic reactions to acid-labile

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food proteins, Dr Jensen-Jarolim's team suggest that PPI may also enable IgE-dependent sensitization to NSAIDs. As PPI are commonly recommended to prevent gastric erosion in patients taking NSAIDs chronically, an interaction between PPI and NSAIDs that may increase the risk of a serious IgE-mediated allergic event merited further investigation.

The researchers in Vienna therefore attempted to replicate the proposed interaction in a mouse model, with intriguing but mixed results [7]. The authors found initially that intragastric challenge with diclofenac with or without gastric acid suppression failed to induce sensitization, as demonstrated by an absence of drug-specific IgE or IgG. Low molecular weight drugs such as diclofenac are not thought to be immunogenic *per se*. Immunogenicity can arise only from their ability to covalently bind to proteins. These modified proteins are then processed and presented to naïve T cells as neo-antigens, evoking an immune response. A true hapten such as penicillin is directly reactive with the protein whereas other drugs are pro-haptens, requiring metabolism by endogenous enzymes to form a protein-reactive intermediate [8]. Individual susceptibility to drug allergy may therefore be related to variability in cytochrome P₄₅₀-dependent metabolic pathways [9]. In both humans and animals, diclofenac is believed to be metabolized via acyl glucuronidation and aromatic hydroxylation to form a number of reactive intermediates, which can then covalently modify self-proteins [10].

In an attempt to augment the immunogenicity of diclofenac, the authors of the report in this issue [7] conjugated the drug to murine serum albumin (MSA) *in vitro* using *N*-hydroxy-succinimide-1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, thus circumventing the requirement for *in vivo* metabolism, and challenged the mice with the conjugate intragastrically. Recently, Jenkinson et al. [11] showed that the contact sensitizer *p*-phenylenediamine (PPD), when conjugated to human serum albumin, can elicit T cell responses in PPD-allergic patients, and in our laboratory we have demonstrated the same using albumin conjugated to the model sensitizer DNCB (unpublished data). The possibility therefore arises that albumin may be one of the main extracellular targets for protein modification *in vivo* by chemical sensitizers; however, there is little evidence in the literature to show that drug-albumin conjugates are effective sensitizers following oral challenge.

Indeed, in the report in the current issue [7], the authors showed that intragastric challenge with the diclofenac-MSA conjugate was unable to induce sensitization on its own, but when administered to mice with concomitant treatment with a proton pump inhibitor (esomeprazole), the diclofenac-MSA conjugate induced sensitization, as detected by the production of diclofenac-specific IgE and IgG. The diclofenac-specific IgE could be used to mediate a

diclofenac-induced degranulation of basophilic leukaemia cells. In addition, it was shown that in the gastric acid suppressed, sensitized mice, subsequent cutaneous challenge with a conjugate of diclofenac and keyhole limpet haemocyanin (KLH) resulted in an immediate inflammatory response. Intriguingly, this cutaneous response was not elicited by monovalent diclofenac alone, suggesting that the diclofenac-specific antibodies recognize the drug only in the context of modified peptide. As the mice were originally sensitized with diclofenac conjugated with MSA, not with KLH, the specificity may be independent of the carrier peptide sequence.

The murine model presented by Dr Riemer et al. [7] clearly shows that sensitization can be induced using drug-modified peptides, thus highlighting the importance of chemically modified food proteins as a source of potential antigens. This would of course be most significant for drugs known to be directly protein reactive, such as penicillins, which do not require biotransformation to form reactive intermediates [12].

The fact that sensitization only occurred after concomitant PPI treatment suggests that high gastric pH is important in protecting acid-labile drug-peptide conjugates from proteolysis. It has been widely documented both in humans and in animal models that an increase in gastric pH induced by PPI or antacid therapies prevents the proteolytic degradation of food proteins in the stomach [13, 14] and presumably facilitates the presentation of food peptides to gut T cells. In this context it is easy to understand how the PPI might have augmented the sensitization to diclofenac-MSA, as it is documented that albumin is proteolytically cleaved by gastric contents [15, 16]. However, there is also evidence that therapies that increase intragastric pH may also preferentially promote T-helper type 2 (Th2) responses [17], possibly through structural changes in the epithelium and villi, and through an increase in eosinophil numbers in the intestine [18].

The wider implication for drug allergy susceptibility is the possibility that PPI or antacid therapies may promote sensitization through the generation of a Th2-biased environment within the gut. This needs to be viewed, however, in the context of how and where a pro-haptenic drug is metabolized to generate the appropriate reactive intermediates, and thus form the modified protein targets required to prime an immune response. In the case of diclofenac, the scenario proposed by Dr Riemer and colleagues would require this pro-haptenic drug both to undergo metabolism to a reactive intermediate and to be conjugated with serum albumin or another peptide within the acid-suppressed stomach before systemic absorption; the failure of diclofenac alone to cause sensitization in acid-suppressed mice suggests that this does not occur, at least in this mouse model. Further work may demonstrate that true haptenic drugs can form direct conjugates with proteins within the stomach, perhaps including food

proteins, and that these potentially immunogenic conjugates are protected from degradation by acid suppressant therapies.

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