

## EDITORIAL

# Clinical & Experimental Allergy

## Facilitation of drug hypersensitivity reactions – the role of acid suppression?

This editorial discusses the findings of the article in this issue by E. Ramirez et al. [1], pp. 344–352.

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Drug hypersensitivity and adverse drug reactions are among the most common clinical problems affecting the general patient population. Between 10% and 15% of patients may suffer from an adverse drug reaction, with 2–5% of these having to be hospitalized, and a reported mortality in up to 1–3% of hospitalized patients [2]. Despite recent advances in our understanding of immunological mechanisms underlying certain drug hypersensitivities, progress remains slow, and insights limited compared with other areas of allergy/immunology. In part, this is due to the very diverse structure of drugs, and their myriad interactions with the immune system via classic immune pathways, or the more recently described direct pharmacological–immunological (p–i) interaction [3]. In addition, genetic susceptibility factors, some of which are just beginning to be understood for a limited number of drugs [4], other drugs as co-factors [5], viral infections [6], exercise and food allergy [7] may interact with drug response and contribute to the variability and apparent unpredictability of clinical manifestations. There is but a limited range of standardized *in vivo* or *in vitro* tests with clinical predictive value that demonstrate the presence of drug-specific IgE or T-lymphocytes. Expert clinical assessment with the judicious application of drug provocation tests remain the foundation and limit of evaluation in most cases of drug hypersensitivity [8]. Initiatives such as the European Network on Drug Allergy (ENDA) [9] and the Drug Hypersensitivity Meetings (DHM) [10] facilitate the sci-

entific dialogue and research necessary to promote advances in this important field.

In this issue of *Clinical & Experimental Allergy*, Ramirez et al. [1] report an intriguing association between the prescription of proton-pump inhibitors and risk of developing of drug hypersensitivity reactions. Using a retrospective nested case–control design of 70 771 tertiary hospital admissions over 2 years, the 166 cases were among possible adverse drug reactions referred to the Allergy Department and confirmed as drug hypersensitivity by the authors. The odds ratio of drug hypersensitivity was 4.35 in hospitalized patients treated with proton-pump inhibitors (PPIs), compared with matched controls after controlling for confounders. Other significant risk factors included a personal history of other drug hypersensitivities and long hospitalization time. The study is well-designed and methodology well-described, including confirmation of cases via detailed clinical evaluation by the authors and their colleagues. The lack of supportive tests reflects the limited availability of evaluation tools as described above, as well as the practicalities of, and indications for, drug provocation challenges. Nevertheless, the rigour of their clinical approach gives some assurance that the cases have largely been correctly identified, within the limits of current best practice. The authors rightly refer to the limitations of a single-centre, retrospective case–control study, restricted to adults, in their discussion of the results. Hence, the interpretation of a possible cause–effect relationship requires caution, with further research in different populations using different methodologies needed to confirm the generalizability of this association.

Pharmacovigilance and pharmaco-epidemiological studies can sometimes reveal insights which lead to improved understanding of underlying immunological mechanisms, and help establish a cause–effect relationship. A recent example is the Scandinavian pholcodine story [11]. Anaphylaxis to neuromuscular blocking

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agents (NMBA) was about 10 times more frequent in Norway than in Sweden, despite social, geographical, and genetic similarities, and identical anaesthetic practices. Sera of Norwegian blood donors was found to contain specific IgE to suxamethonium, the most commonly implicated NMBA in Norway, and to morphine which has a tertiary amine moiety that cross-reacts with the quaternary amine ion (QAI) found in NMBAs [12]. Anaphylaxis to NMBAs can occur on first exposure to the drug, which suggested that the mechanism of sensitization may be another agent with a similar chemical structure. Of the many such household compounds containing QAIs, a cough mixture containing pholcodine was widely used in Norway, but was not available in Sweden. Short-term use of pholcodine was then demonstrated to increase IgE synthesis and levels of specific IgE to suxamethonium and morphine as well as to pholcodine itself. Subsequent withdrawal of pholcodine from the Norwegian market resulted in reduction both of antibody levels and of the incidence of anaphylaxis to NMBAs [13].

Another pharmaco-epidemiological example is the association of paracetamol consumption and risk of developing asthma. The strength of this association is in the consistency of findings between studies of diverse designs in different countries, age-groups, and populations. There is also a plausible biological hypothesis for a causal association with the depletion of glutathione by regular paracetamol ingestion, reducing tolerance of oxidative stress produced by reactive oxygen species (ROS) such as superoxide, and leading to airway injury. The strong evidence for this association

has led to recent calls to urgently establish causation once and for all with adequately powered placebo-controlled trials [14].

The results of Ramirez et al. do not as yet have the strength of the pholcodine and paracetamol associations with NMBA anaphylaxis and asthma risk, respectively, but they open a door with potentially widespread implications. These examples point the way forward to the further research required to establish or refute this association, and the possible cause-effect relationship. There is a biologically plausible mechanism with the modification in drug allergenicity by altering gastric acidity, as well as reasoning by analogy with allergic reactions to acid-labile food proteins. These strengthen the Bradford-Hill criteria for establishing a cause-effect relationship [15]. A question which requires further investigation is whether the relative temporal relationships of commencing the PPIs and the suspected allergenic drug, have an effect on subsequent risk of hypersensitivity reaction i.e. does introducing a suspect allergenic drug before the PPI tolerate the immune system and negate the possible suspected effect of acid suppression on drug allergenicity? These and other research questions are difficult to answer with a retrospective case-control design, and require other experimental approaches. In view of the frequency of use of PPIs, the implications for induction of drug allergy are profound, and further research to address this important question is essential.

**Conflict of interests:** The authors declare no conflict of interests.

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