# Reply

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We welcome the correspondence of Armentia *et al*, as it offers the opportunity to further elaborate on our opposite observations and conclusions. As already exemplified in the introductory paragraph of our study (1), our investigations were initiated because IgE reactivity to morphine and poppy seed (*Papaver somniferum*) is found in 10-15% of specific allergic populations, whereas genuine IgE-mediated allergies for natural occurring opiate alkaloids and (semi)synthetic opioids are exceedingly rare (2). In contrast, many of these compounds are potent non-specific histamine liberators, a property to account for (mostly cutaneous) anaphylactic-like reactions that are much more prevalent than IgE-mediated reactions to these drugs (3). Moreover, in the review by Baldo *et al* (3) some elegant speculations about this intriguing rarity for IgE-mediated opiate and opioid allergy are discussed. Needless to stress that we were somewhat puzzled and frightened by the claims "specific IgE antibodies to whole poppy seed (*Papaver somniferum*) extract, and to a lesser extent also sIgE to morphine to be easy, cheap, simple and useful in the prevention of intraoperative anaphylaxis and hypersensitivity to opiate analgesics" and to constitute "simple and reliable methods to test hypersensitivity to opiates" (4, 5). As a matter of fact, clinically irrelevant sIgE results to poppy seed and morphine could not only lead to an erroneous diagnosis of opiate and/or opioid hypersensitivity, but also, more importantly, lead to the failure to correctly diagnose other drug allergies. For example, a positive sIgE result to morphine, as a biomarker for sensitization to substituted ammonium determinants, could be indicative for a significantly more prevalent rocuronium and/or suxamethonium hypersensitivity (6-8). Moreover, reviewing the anaesthetic records of 100 patients revealed that several cases who demonstrated a positive sIgE to morphine had an uneventful intravenous administration of synthetic opioids such as fentanyl, sufentanil and remifentanil (9).

In their correspondence, the authors argument that our data should be considered as invalid because of several reasons such as the low number of cases, lack of healthy control individuals, lack of provocation tests and the presence of a sensitization to the major allergen from birch pollen Bet v 1.

However, we did not aim at validating tests but rather sought to verify the predictive value of a positive sIgE to morphine and poppy seed. In addition several issues about their studies should be addressed here.

First, in their initial study (4) aimed at assessing the clinical value of sIgE to morphine, pholcodine and poppy seed in people suffering hypersensitivity reactions during anaesthesia or analgesia with from opium-derived drugs and drug abusers with allergic symptoms after heroin injection and to compare usefulness of these 3 determinations as markers of clinical symptoms. Unfortunately the description of some clinical characteristics and laboratory findings in some of these groups is rather incomplete. For example, with respect to the 21 completers in the subgroup of patients who suffered from hypersensitivity during anaesthesia data on the alleged cause are completely missing. Therefore, it cannot be excluded the positive sIgE results for morphine and pholcodine not to be the proof of genuine opiate or opioid hypersensitivity but merely to reflect sensitisation to substituted tertiary or quaternary ammonium epitopes in the context of a hypersensitivity to rocuronium and/or suxamethonium (6-8). Alternatively, in the absence of data about total IgE titers, it cannot be ruled out clinically irrelevant sIgE results to result from non-specific binding to the solid-phase assay. Finally, no correlations between the serologic results and outcome of the poppy seed bronchial provocation test were provided and it is unclear which reference test was finally applied to calculate the predictive values of the sIgE tests. In contrast to the statement in the correspondence letter, authors did not perform challenge tests in all their 203 patients.

Second, in the study published in 2014 (5) the authors sought at comparing the diagnostic accuracy of specific IgE antibodies to morphine, codeine, rocuronium and protein and oil body and aqueous fractions of *Papaver somniferum* seeds in the diagnosis and prevention of allergy to opioids. Although not explicitly stated, from a closer look to the patients' and methods' section, it is likely that the authors have largely enrolled the same patients as described in (4). Therefore, the above-mentioned issues on the poor description of some clinical characteristics and laboratory findings are

applicable again. Moreover, from the description of the patients' population it appears this population to be quite heterogeneous with a majority of the cases probably to have suffered from non-opiate/opioid-related hypersensitivity reactions (e.g. rocuronium, atracurium and propofol). Nevertheless, these patients seem to be included in the "morphine" group.

In their correspondence the authors also argue that none of their patients was Bet v 1 positive and that sensitization towards ns-LTP was not a risk factor for sensitization to morphine. However, we did not claim that sensitization to these components was associated with morphine hypersensitivity, but could be a possible explanation for clinically irrelevant positive poppy seed sIgE results. Unfortunately we were unable to verify our hypothesis, as we failed to locate their data of component resolved diagnosis in their original manuscripts (4, 5).

Finally, it should be notified that no longitudinal data are currently available to endorse the speculative claim that the sensitivity of basophil activation experiments (BAT) in diagnosis of opiate/opioid hypersensitivity might decrease over time. For the potential of BAT in opiate allergy the reader is kindly referred elsewhere (10, 11).

Despite their frequent use, genuine IgE-mediated allergies towards opiates and opioids remain anecdotal. From our observations we believe that the key to correct *in vitro* diagnosis of opiate and opioid allergy lies in elucidating the clinical relevance of sIgE antibody results to morphine, pholcodine and poppy seed. As opiates and opioids seem not to trigger histamine release from human basophils (for review: (3), these cells might become an attractive complementary diagnostic instrument to document genuine IgE-mediated opiate and opioid allergy.

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