

Increased Basal Blood Histamine Levels in Patients with Self-Reported Hypersensitivity to Non-Steroidal Anti-Inflammatory Drugs

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Keywords

Cyclooxygenase inhibitors · Drug hypersensitivity reactions · Histamine · Human peripheral blood · Non-steroidal anti-inflammatory drugs

Abstract

Background: Non-steroidal anti-inflammatory drugs (NSAIDs) represent one of the most prevalent causes of drug hypersensitivity reactions (DHRs), yet the underlying processes are far from clear. Despite the established role of histamine in allergic reactions, its precise implication in DHRs is elusive. **Objectives:** This study aimed to explore the connection of basal blood histamine levels to the reported NSAID hypersensitivity. **Methods:** Sixteen patients reporting hypersensitivity reactions to a single or multiple NSAIDs and/or paracetamol and 18 healthy volunteers serving as the normal control group enrolled in the study. The medical history was recorded and histamine was quantified spectrophotofluorometrically in whole peripheral blood and plasma. **Results:** Compared to the normal group, plasma but not whole blood histamine levels were significantly higher in patients ($p < 0.001$), mainly in the subgroup reporting hypersensitivity to a single agent ($p < 0.001$). Plasma histamine levels were

significantly correlated with the culprit drug selectivity for cyclooxygenase (COX) isozymes ($p < 0.001$), with higher levels being obtained in patients reporting reactions to COX-1 than to COX-2 selective inhibitors ($p < 0.05$). **Conclusions:** The findings provide first evidence connecting basal blood histamine levels to the reported NSAID-triggered DHRs. Prospective studies are expected to decipher the contribution of histamine-associated parameters to the mechanisms underlying DHRs.

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Introduction

Drug hypersensitivity reactions (DHRs) to non-opioid analgesics are unpredictable type B adverse drug reactions of pharmaceutical formulations with a multitude of indications containing non-steroidal anti-inflammatory drugs (NSAIDs), including acetylsalicylic acid (ASA) or paracetamol [1]. These worldwide extensively used medicines are chemically diverse compounds that exert their pharmacological effects predominantly by inhibiting the

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cyclooxygenase (COX) isozymes with different selectivity and potency [2]. NSAID-triggered reactions are among the most frequently reported DHRs, representing more than 20% of the adverse drug reactions that occur in nearly 1.6% of NSAID users [3]. The differential diagnosis of NSAID hypersensitivity is demanding and it typically relies on the frequently non-specific patient history and, occasionally, on skin and/or provocation tests [4]. Commonly, the DHRs to multiple chemically different NSAIDs are regarded as cross-intolerance attributed to non-immunological mechanisms mostly related to COX-1 inhibition, whereas the DHRs to one or more chemically related NSAIDs reflect the contribution of immunoglobulin (Ig) E- and T cell-mediated immunological mechanisms [1, 2, 4].

To a large extent, the complexity of NSAID-triggered hypersensitivity reactions comes from the largely elusive causal mechanisms, as well as from the lack of standardized predictive biomarkers and laboratory tests [1]. Based on the NSAID mechanism of action, most efforts to dissect the etiopathological processes underlying NSAID hypersensitivity evidently focus on the COX-1 hypothesis and the role of eicosanoid mediators, such as leukotrienes and prostaglandins [5]. Although the recognized role of histamine in acute allergic responses and anaphylaxis dates back to the early 20th century [6], its contribution to the DHR etiopathology has not been adequately investigated and only scarce related reports are available [5, 7]. In general, the quantification of plasma histamine may confirm acute IgE-mediated reactions, yet its diagnostic value in anaphylaxis is controversial, mainly due to the short half-life of the amine, its numerous sources, and the demanding measurement methodology [7, 8]. Yet, direct and/or indirect pharmacological or chemical activation of histamine-associated processes may be induced by various drugs, including NSAIDs, often resulting in clinically indistinguishable immune- and non-immune-mediated DHRs [2]. Importantly, accumulating evidence substantiates the implication of histamine in immunomodulation, chronic inflammation, and tolerance in the course of allergic and immune responses [6, 9, 10].

Considering the importance of NSAIDs and paracetamol in all healthcare sectors and the recognized complexity of the currently undefined mechanisms underlying hypersensitivity to these drugs, this pilot real-world study sought to investigate the association of basal whole blood and plasma histamine levels to the reaction history in patients reporting DHRs to NSAIDs and paracetamol.

Materials and Methods

Study Population

A total of 16 adult Caucasian individuals (10 female, 6 male; median age 51 years, range 21–73) with self-reported DHRs to one or more NSAIDs and/or paracetamol were enrolled in the patient group. In this study, DHR refers to both immediate and delayed hypersensitivity to these drugs (Table 1) [1, 2, 4]. The reaction was developed at least 4 days before referral to the outpatient clinic of the Allergy Unit, “Attikon” University Hospital, Athens, Greece. Pregnant or breastfeeding women and patients who had taken antimicrobial agents, antihistamines, and/or corticosteroids during the week prior to blood collection were excluded. The medical records of the patients provided no evidence for atopy or mast cell-related disorders. Eighteen healthy volunteers (8 female, 10 male; median age 35 years, range 19–56) who had previously taken NSAIDs without developing a DHR and received no medication during the week prior to blood collection served as the normal controls.

The patients were assessed by a qualified allergist according to good medical practice [4]. The reported DHRs were grouped as multiple and single NSAID-triggered reactions (Table 2) corresponding to the cross-intolerant and immunological types, respectively [1, 2, 4]. The culprit drugs were ranked as COX-1 selective inhibitors, non-selective COX inhibitors, and COX-2 selective inhibitors based on their COX isozyme inhibitor selectivity (Table 2) following careful pharmacological assessment of the related literature [11].

Histamine Quantification in Whole Peripheral Blood and Plasma

Whole peripheral blood was collected between 10:00 and 14:00 using standard procedures [8]. One aliquot, referred to as whole blood, was stored at -80°C until assayed. Another aliquot was centrifuged within 20 min after collection at 1,400 g for 15 min at 4°C . The supernatant, referred to as plasma, was stored at -80°C until assayed [8, 10]. Whole blood was homogenized with cold HClO_4 prior to histamine extraction. In all samples, histamine was measured spectrophotofluorometrically in duplicate, following extraction and derivatization with *o*-phthalaldehyde [8]. The intra-individual coefficient of variation, based on indicative, daily collected independent samples, was $<8\%$ for plasma and $<6\%$ for whole blood. The coefficient of variation for the test was $<1.3\%$. Histamine levels early after the DHR were not available in this study. However, 4-fold increases are normally detected up to 30 min after the event onset, using the same technique [8, 12].

Statistical Analysis

The statistical analyses were performed using IBM® SPSS® statistics v.25.0 using the appropriate descriptive and inferential tests as indicated in the results. Histamine values are expressed as the mean $\pm$ standard deviation (SD). A value of $p < 0.05$ was considered significant with a 95% confidence interval.

Results

In the patient group, plasma histamine levels were significantly higher than in normal subjects (8.66 ± 4.13 vs. 3.61 ± 1.32 ng/mL of blood, respectively; $p < 0.001$, inde-

Table 1. Demographic and clinical data on the patients reporting hypersensitivity reactions to NSAIDs and/or paracetamol

Patient No.	Gender	Age, years	Culprit drug(s)	Onset ^a , h	Distance ^b	Clinical manifestations	Comorbidities ^c
1	M	29	Paracetamol	<1	45 days	Urticaria, angioedema	Irritable bowel syndrome
2	M	48	ASA, etoricoxib, mefenamic acid, niflumic acid	<1	Approx. 2 years	Pruritus, erythema, dyspnea, throat tightness	Ankylosing spondylitis, hypertension, fibromyalgia, persistent rhinitis
3	F	47	ASA, mefenamic acid, etoricoxib, nimesulide, paracetamol	<1	1 year	Urticaria, angioedema	Hypothyroidism, anemia
4	M	49	Indomethacin	1–6	2 years	Urticaria, dyspnea, fatigue	Arrhythmias, diabetes
5	F	53	Naproxen	>6	2 years	Urticaria, angioedema	Chronic diarrhea, dyslipidemia, thyroiditis
6	F	43	Oxaprozin	1–6	2 weeks	Angioedema	Hashimoto disease
7	F	66	ASA, mefenamic acid	<1	>15 years	Pruritus, angioedema, dyspnea, hoarseness, hypotension, vomiting	No
8	F	73	ASA	1–6	3 months	Angioedema	No
9	M	42	ASA, diclofenac	1–6	1 month	Angioedema	No
10	M	72	ASA, lornoxicam	1–6	1 month	Angioedema	Hypertension, dyslipidemia
11	F	62	ASA, diclofenac	1–6	>25 years	Angioedema	COPD, hypertension
12	F	70	Mefenamic acid	<1	ND	Urticaria, vomiting, diarrhea, loss of consciousness	Hypertension
13	F	67	Diclofenac	1–6	4 days	Angioedema	G6PD deficiency
14	F	56	Etoricoxib, nimesulide	>6	1 month	Fixed drug eruption	CVI, diabetes
15	F	21	ASA, ibuprofen	ND	1 week	Dyspnea, bronchoconstriction	No
16	M	45	Lornoxicam	<1	5 years	Pruritus, angioedema, hoarseness	Hypertension, dyslipidemia, depression

ASA, acetylsalicylic acid; COPD, chronic obstructive pulmonary disease; CVI, chronic venous insufficiency; M, male; F, female; G6PD, glucose-6-phosphate dehydrogenase; ND, not defined. ^a Minimum interval between drug intake and reaction. ^b Minimum interval between reaction and blood sampling. ^c At the time of blood sampling.

pendent samples *t* test; Fig. 1a). Multiple regression analysis showed that gender, age, and the presence of chronic conditions were not associated with the plasma histamine levels ($R^2 = 0.285$, $p > 0.5$). Similarly, the DHR characteristics, including the clinical manifestations and the number of the culprit agents, had no significant combined effect on the plasma histamine levels ($R^2 = 0.271$, $p > 0.3$). Moreover, plasma histamine levels were not significantly correlated with the time interval between the manifestation of the reaction and drug intake (Spearman's $\rho = 0.172$, $p > 0.5$) or blood sampling (Spearman's $\rho = 0.207$, $p > 0.1$).

Interestingly, however, plasma histamine levels differed significantly between the normal group and the subgroups of patients with reported reactions to a single or to multiple drugs, the median values being 3.96 ng/mL of blood (range 1.41–6.13), 10.42 ng/mL of blood (range 6.44–16.51), and 5.77 ng/mL of blood (range 2.71–13.90), respectively ($p < 0.001$, Kruskal-Wallis H test; Fig. 1b). Post hoc analysis demonstrated that plasma histamine levels in patients reporting reactions to a single agent were significantly higher than in normal subjects ($p < 0.001$, Dunn's pairwise test; Fig. 1b). No significant differences

Table 2. Frequencies of the DHRs to NSAIDs based on the number of culprit drug(s) and their selectivity for COX isozyme inhibition

Characteristic	Patients, <i>n</i> (% of total)
Single NSAID-induced hypersensitivity reactions	8 (50.00)
Multiple NSAID-induced hypersensitivity reactions	8 (50.00)
DHRs to COX-1 selective inhibitors	3 (18.75)
DHRs to non-selective COX inhibitors	3 (18.75)
DHRs to COX-2 selective inhibitors	3 (18.75)
DHRs to multiple NSAIDs within different selectivity for COX	7 (43.75)

DHRs, drug hypersensitivity reactions; NSAID, non-steroidal anti-inflammatory drug; COX, cyclooxygenase.

were obtained between the patients reporting DHRs to multiple drugs and the normal group or the individuals with DHRs to a single agent ($p > 0.3$, Dunn's pairwise test; Fig. 1b). The patients' gender and age and the presence of comorbidities were not associated with the plasma histamine levels in any subgroup ($p > 0.05$, regression analysis). Likewise, no connection was found in any subgroup between histamine levels and the reported reaction onset or clinical symptoms ($p > 0.1$, regression analysis).

A total of 9 (56.25%) of the reactions were triggered by one or more agents that could be grouped according to their selectivity for the COX isozymes (Table 2). Plasma histamine levels were negatively correlated with the culprit drug selectivity toward inhibition of the inducible COX-2 isozyme (Spearman's $\rho = -0.949$, $p < 0.001$). Histamine levels were significantly different between the subgroups of patients reporting hypersensitivity to COX-1 selective, non-selective, and COX-2 selective NSAIDs, the median values being 13.06 ng/mL of blood (range 11.81–16.5), 10.01 ng/mL of blood (range 7.16–10.74), and 6.44 ng/mL of blood (range 5.92–6.63), respectively ($p < 0.05$, Kruskal-Wallis H test; Fig. 1c). Post hoc analysis showed that plasma histamine levels were significantly higher in patients reporting reactions to COX-1 than to COX-2 selective inhibitors ($p < 0.05$, Dunn's pairwise test; Fig. 1c).

Whole blood histamine levels in both the normal and the patient groups were significantly higher than the respective plasma values ($p < 0.001$, paired samples *t* test), whereas whole blood levels were not significantly correlated with the plasma values or with the age and gender of the subjects in either the normal or the patient group ($p > 0.05$, Pearson correlation). In contrast to plasma, no significant differences in whole blood histamine levels were obtained between the normal and the patient group ($p > 0.1$, independent samples *t* test; Fig. 2d). Gender, age,

and the presence of chronic conditions were not associated with the whole blood histamine levels ($R^2 = 0.029$, $p > 0.5$, multiple regression analysis). Similarly, the DHR characteristics had no significant combined effect on whole blood histamine levels ($R^2 = 0.134$, $p > 0.2$, multiple regression analysis), which were not significantly correlated with the anamnestic time interval between the manifestation of the reaction and drug intake (Spearman's $\rho = -0.278$, $p > 0.3$) or blood sampling (Spearman's $\rho = 0.382$ respectively, $p > 0.1$).

Contrary to plasma, whole blood histamine levels were not different between the normal group and any of the patient subgroups reporting reactions to a single or to multiple NSAIDs ($p > 0.1$, Kruskal-Wallis H test; Fig. 1e). Moreover, no relationship was found between whole blood histamine levels and NSAID selectivity for COX isozymes (Spearman's $\rho = -0.527$, $p > 0.1$; Fig. 1f).

Discussion

The findings highlight the significant increases in the basal levels of circulating histamine in the blood plasma of individuals who reported hypersensitivity to NSAIDs and/or paracetamol compared to those who did not (Fig. 1a). A more detailed data analysis revealed that, contrary to the individuals reporting multiple NSAID-induced reactions, plasma histamine levels in patients reporting single NSAID-induced hypersensitivity reached statistical significance compared to healthy individuals (Fig. 1b). Although the size of the study population was small, the value of these novel data comes from the fact that they are derived from a real-world investigation in the routine clinical practice of a tertiary referral allergy unit [13].

The likely connection of basal histamine levels and/or histamine-related processes to NSAID hypersensitivity

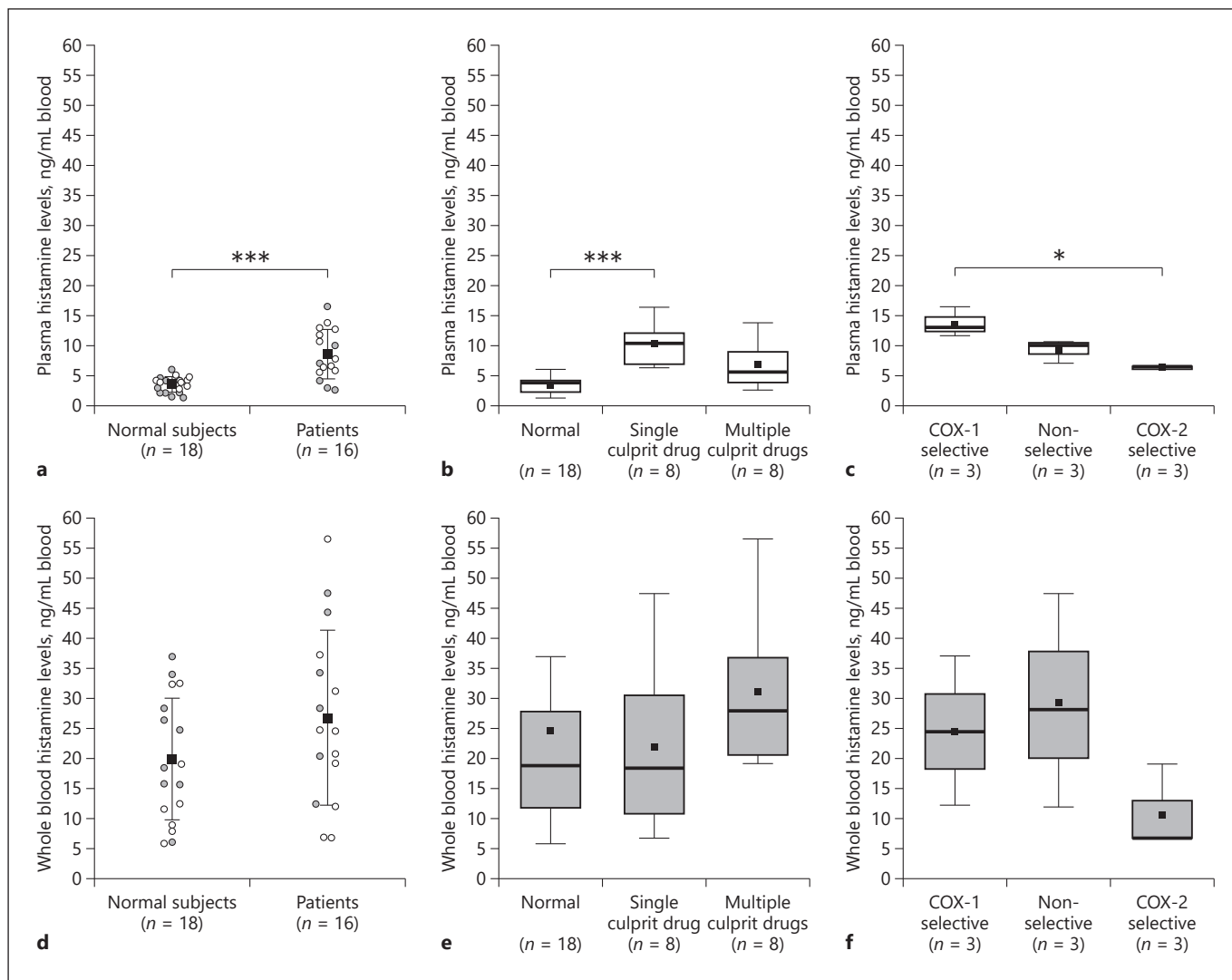


Fig. 1. Histamine levels in plasma (a–c) and whole blood (d–f) samples obtained from healthy (normal) subjects and from patients reporting hypersensitivity reactions to NSAIDs or paracetamol. **a, d** Data are shown as the mean $\pm$ SD. Scattered points represent individual values in male (closed circles) and female (open circles) subjects. Plasma (**b**) and whole blood (**e**) histamine

levels in patients reporting hypersensitivity reactions to a single or to multiple NSAIDs and/or paracetamol. Plasma (**c**) and whole blood (**f**) histamine levels in patients reporting hypersensitivity reactions to COX-1 selective, non-selective, and COX-2 selective inhibitors. Black squares indicate mean values. * $p < 0.05$, *** $p < 0.001$ between the indicated groups, respectively.

has been suggested by an earlier study reporting increased basal plasma histamine levels in patients with a history of ASA-induced urticaria and/or angioedema [7]. Furthermore, increased frequency of the diamine oxidase (DAO) activity-reducing DAO 16Met variant has been observed in Caucasians with clinical symptoms of NSAID hypersensitivity [14].

Although the endogenous modulatory processes and/or the cellular sources that may result in the elevated plasma histamine in NSAID hypersensitivity are unclear, the

possible involvement of mast cells and basophils is an obvious source to consider. Sporadic reports failed to provide solid evidence linking lasting mast cell activation to ASA hypersensitivity [5], whereas the hypothesis of a direct NSAID effect on the IgE-mediated mast cell and basophil activation remains to be confirmed [2]. Higher basal tryptase levels were recently reported in patients with severe compared to mild-moderate anaphylaxis, but these differences were not specifically associated to the different types of triggers, including various drugs [15].

Considering the absence of evidence indicative of atopy, mast cell-related comorbidities and severe DHRs in the study population (Table 1), this investigation focused on the putative association of diverse NSAID-triggered reactions to circulating histamine, independently of its cellular source or degradation processes [15, 16]. Nevertheless, the fact that basal tryptase and DAO levels may be determinants of DHRs to NSAIDs in patients with or without an underlying disease would be an interesting hypothesis to explore in the future.

Importantly, however, the increased basal plasma histamine levels correlated well with the selectivity of the culprit drug(s) towards the inhibition of the constitutive COX-1 (Fig. 1c). This may reflect alterations in the tonic production and release, and hence in the non-redundant cross-talk, of the inflammatory eicosanoid mediators and histamine derived, among others, from naïve basophils and mast cells in individuals developing DHRs [17]. This is supported by the differences in the time course of the production and release of these effector molecules in allergic inflammation that may be driven, at least in part, by differential COX-1 and COX-2 expression and induction [17]. However, the findings should be interpreted with caution for various reasons. Besides the relatively small sample size, the fact that this work targeted self-reported DHRs should be considered, since any related bias cannot be ruled out. Moreover, there are inherent limitations in defining the relative ranking of NSAID selectivity for the COX isozymes, as the existing literature relies on multiple *in vitro* models of COX isozyme inhibition with marked variability of the pharmacological properties among NSAIDs in various cells, and tissues under physiological and pathological conditions are repeatedly overlooked [11].

On the other hand, it should be noted that the profile of the whole blood histamine levels was not comparable to that observed in plasma, with the respective values exhibiting greater variability and overlap in both the normal and the patient groups (Fig. 1). Thus, alternative or complementary, yet undetermined, factors and/or endotypes may moderate the homeostatic balance between circulating and stored histamine in peripheral blood, driving NSAID hypersensitivity in susceptible individuals. Given the growing evidence on the immunomodulatory role of histamine in chronic inflammation [9] and in allergen tolerance [10], a putative link between blood histamine and DHR-related endotypes is currently under consideration.

To our knowledge, this is the first real-world study to explore the implication of basal circulating histamine to NSAID hypersensitivity. The findings indicate that elevated blood plasma histamine levels at the basal state may

be a common factor characterizing the development of hypersensitivity reactions to NSAIDs and/or paracetamol. Moreover, they point to the association of blood histamine with the selectivity of the culprit drug(s) towards the inhibition of the constitutive COX-1 isozyme. The data presented in this preliminary study are expected to provide a fundamental lead for designing cohorts based on DHR diagnosis confirmation and clinical sub-classification, and to guide prospective studies on the biological relevance and the clinical value of histamine-associated parameters that likely contribute to the etiopathology of DHRs.

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Statement of Ethics

All participants signed an informed consent. The procedures were performed in accordance with the Declaration of Helsinki and Greek ethical law, and approved by the ethics committee of the Medical School NKUA (1516031202/01.07.16). Personal data were handled in line with the European GDPR 2016/679.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.K., F.S., and E.T. designed the study and contributed to the results interpretation. M.K. conducted the experiments. M.K. and E.T. performed the statistical analyses and drafted the manuscript. A.K., C.C., and M.M. performed the clinical evaluations and sample collection. E.T. conceived and guided the investigation. All authors revised the manuscript and approved the final version.

References

- 1 Blanca-López N, Somoza-Alvarez ML, Bellon T, Amo G, Canto G, Blanca M. NSAIDs hypersensitivity: questions not resolved. *Curr Opin Allergy Clin Immunol*. 2018 Aug;18(4):291–301.
- 2 Pham DL, Kim JH, Trinh TH, Park HS. What we know about nonsteroidal anti-inflammatory drug hypersensitivity. *Korean J Intern Med (Korean Assoc Intern Med)*. 2016 May;31(3):417–32.
- 3 Blumenthal KG, Lai KH, Wickner PG, Goss FR, Seger DL, Slight SP, et al. Reported incidence of hypersensitivity reactions to nonsteroidal anti-inflammatory drugs in the electronic health record. *J Allergy Clin Immunol*. 2016;137(2 suppl):AB196.
- 4 Kowalski ML, Makowska JS, Blanca M, Bavbek S, Bochenek G, Bousquet J, et al. Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) - classification, diagnosis and management: review of the EAACI/ENDA(®) and GA2LEN/HANNA. *Allergy*. 2011 Jul;66(7):818–29.
- 5 Mita H, Endoh S, Kudoh M, Kawagishi Y, Kobayashi M, Taniguchi M, et al. Possible involvement of mast-cell activation in aspirin provocation of aspirin-induced asthma. *Allergy*. 2001 Nov;56(11):1061–7.
- 6 Tiligada E, Ennis M. Histamine pharmacology: from Sir Henry Dale to the 21st century. *Br J Pharmacol*. 2018. doi: 10.1111/bph.14524.
- 7 Asad SI, Murdoch R, Youlten LJ, Lessof MH. Plasma level of histamine in aspirin-sensitive urticaria. *Ann Allergy*. 1987 Sep;59(3):219–22.
- 8 Tiligada E, Kakolyri M, Ennis M. Histamine quantification in human blood samples. In: Tiligada E, Ennis M, editors. *Histamine receptors as drug targets*. New York: Springer; 2017. pp. 489–508.
- 9 O'Mahony L, Akdis M, Akdis CA. Regulation of the immune response and inflammation by histamine and histamine receptors. *J Allergy Clin Immunol*. 2011 Dec;128(6):1153–62.
- 10 Chliva C, Aggelides X, Makris M, Katoulis A, Rigopoulos D, Tiligada E. Comparable profiles of serum histamine and IgG4 levels in allergic beekeepers. *Allergy*. 2015 Apr;70(4):457–60.
- 11 Knights KM, Mangoni AA, Miners JO. Defining the COX inhibitor selectivity of NSAIDs: implications for understanding toxicity. *Expert Rev Clin Pharmacol*. 2010 Nov;3(6):769–76.
- 12 Makris M, Aggelides X, Chliva C, Katoulis A, Papamichael K, Tiligada E. High baseline blood histamine levels and lack of cross-reactivity in a patient with ranitidine-induced anaphylaxis. *J Investig Allergol Clin Immunol*. 2014;24(5):361–3.
- 13 Evans K. Real World Evidence: can we really expect it to have much influence? *Drugs Real World Outcomes*. 2019 Jun;6(2):43–5.
- 14 Agúndez JA, Ayuso P, Cornejo-García JA, Blanca M, Torres MJ, Doña I, et al. The diamine oxidase gene is associated with hypersensitivity response to non-steroidal anti-inflammatory drugs. *PLoS One*. 2012;7(11):e47571.
- 15 Aniceto V, Dias MM, Melo JM, Trevisan-Neto O, Aragon DC, Maia LS, et al. Serum baseline tryptase level as a marker for the severity of anaphylaxis. *Int Arch Allergy Immunol*. 2019;179(3):201–8.
- 16 Boehm T, Reiter B, Ristl R, Petroczi K, Sperr W, Stimpfl T, et al. Massive release of the histamine-degrading enzyme diamine oxidase during severe anaphylaxis in mastocytosis patients. *Allergy*. 2019 Mar;74(3):583–93.
- 17 Bando T, Fujita S, Nagano N, Yoshikawa S, Yamanishi Y, Minami M, et al. Differential usage of COX-1 and COX-2 in prostaglandin production by mast cells and basophils. *Biochem Biophys Res*. 2017 Mar;10:82–7.