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DRUG-INDUCED ANAPHYLAXIS UNCOMMON IN MASTOCYTOSIS: FINDINGS FROM TWO LARGE COHORTS

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1 **DRUG-INDUCED ANAPHYLAXIS UNCOMMON IN MASTOCYTOSIS:**

2 **FINDINGS FROM TWO LARGE COHORTS**

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34 The authors declare that the research was conducted in the absence of any commercial or financial
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ABSTRACT

Background: Anaphylaxis is a common feature of mastocytosis patients, particularly with Hymenoptera venoms. Hence, it is hypothesized that mastocytosis patients may have an increased susceptibility to developing drug-induced anaphylaxis (DIA). Patients and medical practitioners are therefore concerned when there is a need to use various drugs. However, this issue has not been systematically investigated.

Objective: Our study aimed to investigate the prevalence and clinical characteristics of anaphylaxis to various types of drugs among mastocytosis patients.

Methods: A retrospective study was conducted among 470 consecutive patients (≥ 18 years) with confirmed clonal mast cell diseases recruited from two independent mastocytosis reference centers. All patients underwent a comprehensive, individualized allergy workup with evaluation of the (self)reported drug hypersensitivity.

Results: Overall prevalence of DIA was 6.3% accounting for 1/3 of the confirmed drug hypersensitivity reactions. Non-steroidal anti-inflammatory drugs (NSAIDs) were the most common elicitors of DIA (56%), followed by perioperative agents (23%) and antibiotics (13%). Anaphylactic reactions were severe in most cases with 43% of patients experiencing hypotensive syncope. All drug-related hypersensitivity reactions occurred before mastocytosis was diagnosed.

Conclusions: The prevalence of DIA in mastocytosis tends to be higher than in general population, but is overall low. However, its severity is more pronounced. Our results suggest that mastocytosis patients with a prior reaction to drugs should undergo a thorough allergy workup. Well-tolerated drugs can be further used without specific precautions.

Highlights box

What is already known about this topic? Mastocytosis patients are susceptible to severe anaphylaxis, particularly with Hymenoptera stings. It is hypothesized that ingestion of certain drugs may also cause more often severe immediate hypersensitivity reactions.

What does this article add to our knowledge? Our findings indicate that drug-induced anaphylaxis tends to be higher in mastocytosis patients compared to the general population; nevertheless, overall prevalence is still low.

How does this study impact current management guidelines? Our results support the recommendation that mastocytosis patients with a prior reaction to drugs can benefit from a thorough allergy workup; however, previously well-tolerated drugs can be further used without specific precautions.

Keywords

Anaphylaxis. Drug hypersensitivity. Mastocytosis. KIT D816V. Tryptase. NSAID. Antibiotics. Perioperative drugs.

Abbreviations

BAT – Basophil activation test

BM – Bone marrow

CM – Cutaneous mastocytosis

DCT – Drug challenge test

DHR – Drug hypersensitivity reaction

DIA – Drug-induced anaphylaxis

IDT – Intradermal drug test

MC – Mast cell

MIS – Mastocytosis in the skin

MMAS – Monoclonal mast cell activation syndrome

NMBA – Neuromuscular blocking agent

NSAID – Non-steroidal anti-inflammatory drugs

PCV – Penicillin V

sBT – Serum baseline tryptase

SM – Systemic mastocytosis

SPT – Skin prick test

UA – Unprovoked anaphylaxis

VIA – Venom induced anaphylaxis

Introduction

Drugs are one of the predominant causes of anaphylaxis in adults, especially in hospitalized patients (1-3). Most severe reactions are immediate and happen within 1-6 hours from the last administration (4,5). Antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently reported culprits in drug hypersensitivity reactions (DHRs) and account for most fatalities (1-3). However, data about prevalence/incidence of drug-induced anaphylaxis (DIA) in the general population are scarce. An American electronic health records' survey of 1,756,481 adults, reported 19,836 (1.1%) cases of DIA among 622,152 with at least one reported DHR (6). Similarly, other studies estimated that drugs account for 35% (7) and 42% (8) of identified anaphylaxis cases. Furthermore, although DIA can be triggered in all ages, the frequency tends to be related to age, presumably due to a higher use of medications (1), and females are more susceptible to experience DIA than men (1,3).

Mastocytosis is a rare, heterogeneous group of disorders characterized by accumulation and activation of clonally aberrant mast cells (MCs) in different tissues, preferentially in the skin, and bone marrow (9,10). In general, mastocytosis may be systemic (SM) or cutaneous (CM). In adults, SM often manifest as a systemic disease with cutaneous lesions. Diagnosis of SM can be made after an extra-cutaneous biopsy and in patients with monoclonal MC activation syndrome (MMAS), the World Health Organization (WHO) criteria for SM are not fully met (9,10). Notably, anaphylactic reactions are a well-known feature of adults with SM, which may depend on the combination of increased MC burden, inherent hyperreactivity and increased releasability of clonally aberrant MCs in these patients (11-13). Elicitors of anaphylaxis in mastocytosis most commonly include Hymenoptera stings (14), whereas food-induced anaphylactic reactions seem to be less common (15). It has also been assumed that mastocytosis patients may have an increased susceptibility to develop DIA. However, this issue has not yet been systematically investigated. Most of the previous reports were associated with the specific drugs, such as NSAIDs (16-18), antibiotics (19), perioperative drugs (20-22), local anesthetics (23), radiocontrast media (RCM) (24), and vaccines (25-27).

Hence, there is an unmet need to investigate the safety of implicated drugs in mastocytosis. We therefore aimed to explore the prevalence and clinical characteristics of anaphylaxis to drugs among a large cohort of mastocytosis patients recruited from two European reference centers. Furthermore, we sought to analyze the culprit drugs and to explore whether the frequency and severity of reactions are influenced serum baseline tryptase (sBT) levels, total IgE, atopic status/disease, gender, or variant of mastocytosis.

Methods

Study design and settings

We conducted a two-center retrospective cohort study among mastocytosis patients diagnosed and treated at the Mastocytosis Center Karolinska, Stockholm, Sweden, and the Antwerp Mastocytosis Center, Antwerp University Hospital, Antwerp, Belgium. A total of 470 adult patients were enrolled in this study.

The diagnosis of mastocytosis was obtained, in accordance with WHO-criteria (9,10). Diagnostic workup included histopathological evaluation of bone marrow (BM), flow cytometry, *KIT* D816V mutation analysis, and measurement of sBT. Moreover, all patient-reported drug reactions were evaluated by allergists before considering them DHRs. Patients with isolated gastrointestinal symptoms or vague complaints such as isolated fever, nausea, headache, malaise were excluded. A more detailed review of the medical records was performed for individuals with possible DIA by two experienced allergists (VS and TG, and in case of disagreement DE) to ensure that the diagnostic criteria for anaphylaxis were fulfilled (28). Atopy was defined as a positive skin prick test (SPT) to at least one of the usually tested aeroallergens or a positive IgE test to the inhalant, Phadiatop® (ImmunoCAP®, ThermoFisher, Uppsala, Sweden). Patients with atopic diseases (asthma and/or rhinitis) were identified among patients with confirmed atopy. Atopy was routinely assessed in the Swedish but not in the Belgian cohort.

The diagnosis of anaphylaxis was based on clinical presentation, supported by acute serum tryptase measurement when available. Exposure within 1 hour (often minutes) was used to assess causality. All the cases were re-evaluated by experienced allergist before being validated.

Study subjects

The Swedish cohort

The Mastocytosis Center Karolinska was established in 2006 at Karolinska University Hospital, and 681 consecutive adults (>18 years), as of December 31st, 2022, had been referred to the center because of suspected mastocytosis. Of investigated patients, a total of 284 were diagnosed having mastocytosis according to current WHO-criteria (9,10). Of those, 252 provided a written informed consent for enrollment in the study (Figure 1). Ethical approval was obtained from the Regional Ethical Review Board, Stockholm, Sweden (approval no. 2011/1750-31/3 and 2018/2621-31). Median follow-up from diagnosis was 9 years (range 1.5 - 23 years).

All enrolled patients underwent standardized allergy work-up at the Respiratory Medicine and Allergy outpatient clinic, including detailed medical history and allergy tests, e.g., SPT and/or specific IgE (sIgE) antibody test (ImmunoCAP®), to assess the presence/absence of atopy, as previously described (14). Total IgE and sBT were measured in all patients. In addition, detailed information regarding demographics, atopic status, history of previous hypersensitivity reactions to antibiotics, analgesics and NSAIDs, local anesthetics, general anesthesia, RCM, opiates and vaccines, as well as clinical manifestations and outcomes were obtained. When available, information on administration type and time elapsed between drug intake and start/onset of symptoms were also evaluated. Moreover, the possible effect of concomitant triggers, such as physical exertion, heat, cold, emotional stress, or intake of alcohol, were carefully assessed as potential confounders. Afterwards, the likelihood of a possible drug hypersensitivity and DIA were identified by an experienced allergist (TG).

The Belgian cohort

Similarly, comparative data of 218 patients with mastocytosis as per WHO criteria from the Antwerp Mastocytosis Center, an independent cohort, were obtained. The study was approved by the institutional review board (B300201836890) and all enrolled patients signed an informed consent. An allergy work-up to assess the presence/absence of atopy was not systematically performed; however, analysis of total IgE levels was available in most patients. Among patients with reported drug reactions, drug hypersensitivity was assessed, and DIA was identified and re-evaluated by an experienced allergist (VS) before confirming the final diagnosis (Figure 1). Median follow up-time was 5 years (range 1 - 23 years)

Moreover, data from additional cohorts of patients with DIA without clonal disorders from both centers were included to compare with mastocytosis patients with DIA. In the Swedish cohort, there were 396 non-clonal patients who were referred due to suspected mast cell disorders (for instance, on the basis of elevated baseline serum tryptase, and/or history of any kind of anaphylaxis). They underwent exactly the same investigation procedures as the patients in the study cohort; however, a mastocytosis diagnosis was ruled out. For the Belgian cohort, a total of 153 patients with confirmed DIA were used for comparison with the clonal group. Patients of these special cohort were all referred by anaesthesiologists because of perioperative hypersensitivity reactions.

Drug hypersensitivity diagnostic work-up

Skin testing and, when available, sIgE and BAT (in the Belgian cohort) were used to assess the underlying mechanism. In one case, a challenge test was used to confirm causality. In the case of perioperative anaphylaxis, challenges were performed with all exposed drugs (except anesthetics) that tested negative in the allergy work-up if a cause was identified. The diagnostic work-up for DIA was mostly performed when the diagnosis of mastocytosis was already known. In only 2 patients, the diagnosis of mastocytosis was established after DIA.

Skin tests

SPTs and IDTs were performed on the ventral part of the forearm for all potential culprit drugs if applicable. SPT with histamine 10 mg/mL (HAL AllergyBenelux BV, Leiden, the Netherlands) and saline buffer were used as positive and negative control, respectively. After 15 minutes, the SPTs were read and considered positive if the wheal and flare reaction exceeded 3 mm. Patients with negative SPTs had additional serial dilutions of IDTs. For all tested compounds except NMBAs, IDT was considered positive if the wheal equaled or exceeded 5 mm or when the wheal had doubled compared with the injection bleb induced by 0.02 mL of the tested solution. For NMBAs, IDT was considered positive when the wheal equaled or exceeded 8 mm or when the wheal had doubled compared with the injection bleb with surrounding erythema.

Serology

Total and sIgE antibodies were quantified by using the ImmunoCAP FEIA technique (Phadia Thermo Fisher, Uppsala, Sweden). The cutoff for positivity were used as recommended by the manufacturer (i.e., 0.10 or 0.35 kUA/L).

Drug challenge test

Drug challenge test (DCT) with the index drugs was not routinely performed, as the patients declined it due to safety reasons. However, one Swedish patient, who mildly reacted to penicillin V, underwent an oral DCT with the suspected culprit and experienced anaphylaxis with syncope. Subsequent investigations disclosed that this patient had SM.

Statistical analysis

IBM SPSS Statistics 28.0 (SPSS Inc., Chicago, IL, USA) was used to perform statistical analysis. A p-value < 0.05 was considered statistically significant. Continuous variables were presented by median values and ranges, and categorical variables were displayed as frequencies and percentages. Because the data are not normally distributed, Kruskal-Wallis's test was used to compare continuous variables from three groups, i.e., patients with DIA, venom-induced anaphylaxis (VIA), and unprovoked anaphylaxis (UA), and Mann-Whitney *U*-test was used in case of comparison between two groups (i.e., mastocytosis vs. MMAS, and clonal DIA vs. non-clonal DIA). Chi-Square test or Fisher's exact test was used to analyze qualitative (i.e., categorical) variables when suitable.

Results

Characteristics of study subjects

Baseline characteristics of participants from both cohorts are separately shown in Table 1. In the Swedish cohort, 188 patients met the diagnostic criteria of SM and an additional 16 patients were diagnosed as mastocytosis in the skin (MIS), as they refused to undergo a BM-investigation. Another 48 patients were diagnosed with MMAS as they fulfilled only 1 or 2 WHO criteria for SM. Similarly, in the Belgian cohort, 135 patients were diagnosed with SM, 19 MIS and 64 MMAS (Table 1). In both centers, most SM patients had the indolent variant of the disease (93% in the Swedish and 96% in the Belgian cohort, respectively). Likewise, coexistence of the mastocytosis related skin lesions was found 61% in the Swedish and 63% in the Belgian cohort (Table 1). Furthermore, gender division was similar, i.e., with 46% male in the Swedish and 44% male in the Belgian cohort. Median age at diagnosis was also similar across both cohorts, 52 years in the Swedish cohort and 49 years in the Belgian.

Furthermore, median sBT levels for the Swedish cohort was 24.5 ng/mL (range 3 - 650) and 20.2 ng/mL (range 7 - 505) for the Belgian. Levels were highest in the SM group in both cohorts (30 ng/mL and 20.9 ng/mL, respectively). Median total IgE (kU/L) was 19 (range 1-1,600) in the Swedish cohort and 41 (2 - 1,189) in Belgian cohort. In the Swedish cohort, atopy and atopic diseases, such as asthma and rhinoconjunctivitis, were present in nearly 30% of all patients (Table 1). Interestingly, both mastocytosis cohorts include anaphylaxis-prone patients, as a history of anaphylaxis was similar across cohorts (54% in the Swedish cohort, 49% in the Belgian) (Table 1).

Prevalence of DIA

Of the 252 Swedish mastocytosis patients, 58 (23%) patients with DHRs were confirmed after re-evaluation by the allergist. Of those 58, 10 patients (4%) were deemed to have experienced a DIA (Table 2). In addition, among 135 patients with confirmed anaphylaxis (by any trigger), only 10 (7.4%) were caused by drugs. Likewise, in the Belgian cohort, 28/218 (12.8%) patients were identified to have experienced a DHR after an allergy workup. Twenty of them (9.1% of the cohort) were considered to have experienced DIA. With regard to Belgian cohort drugs accounted for 20/107 (18.7%) of anaphylactic reactions. When comparing SM patients with MMAS patients, there were no significant differences regarding the prevalence of DIA or DHRs, although MMAS patients exhibited a higher prevalence of DIA in both cohorts (Table 2).

Clinical features of patients with DIA

The clinical characteristics of individual patients with DIA in both cohorts are described in detail in Table 3. Of the 10 Swedish patients with DIA, 7 were diagnosed with ISM and 3 as a MMAS. Additionally, a significant increase in tryptase level in concomitance of the anaphylactic reaction was confirmed in 50% (5/10) of the DIA-cases. In the Belgian cohort, 12 of the 20 DIA patients had diagnosis of SM, whereas 7 had MMAS and 1 had MIS. Moreover, anaphylaxis was confirmed by event-related elevation in tryptase levels in 9 of 20 patients (45%) in this cohort. All DIA reactions occurred prior to diagnosis of mastocytosis, and notably, no additional reactions were reported during the post-diagnostic follow-up period, as patients avoided culprit drugs.

Clinical presentation of DIA was similar in both cohorts. Cardiovascular symptoms (i.e. hypotension) were the most common and presented in 30/30 (100%) cases, followed by cutaneous symptoms in 15/30 (50%) cases. Respiratory symptoms occurred in 10/30 (33%) of the cases, and gastrointestinal symptoms, where reported only in 4/30 (13%). Notably, anaphylaxis led to hypotensive syncope in

13/30 (43%) patients (Table 3). In addition, with regard to gender, 16/30 (53%) patients with DIA were males in the overall cohort.

Culprit Drugs

NSAIDs were the most frequent culprits of DIA accounting for 50% of the reactions in the Swedish and 60% in the Belgian cohort, respectively (Figure 2). Among the NSAIDs, diclofenac was the most common culprit drug (3 of 5 reactions) in the Swedish cohort, meanwhile in the Belgian cohort ibuprofen was predominating (7 of 12 reactions). None of the patients underwent a challenge test with the suspected index NSAID. In Belgian cohort all the patients tolerated a (partial) selective COX-2 inhibitors (meloxicam, celecoxib, etoricoxib).

In addition, 30% of the DIA reactions were attributable to perioperative drugs in the Swedish cohort, whereas these drugs accounted for 20% of the DIAs in the Belgian cohort. The neuromuscular blocking drug atracurium was the most prevalent culprit in the Swedish cohort (2 of the 3 reactions). Rocuronium was the most common (2 of 4 reactions) in the Belgian cohort. No antibiotics were identified as culprit in any of the cases with perioperative anaphylaxis.

Antibiotics elicited DIA in 20% of the Swedish, and 10% of the Belgian cohort. Penicillin was the triggering drug in both Swedish cases, confirmed by a positive SPT in the first case, and through a positive drug provocation test with presence of penicillin-specific IgE-antibodies in the second case (Table 3).

Comparative analysis of DIA

We have assessed potential risk factors for developing DIA in mastocytosis patients. In the Swedish cohort, none of the patients with DIA had an atopic predisposition and this was statistically significant when compared to patients with history of VIA and UA (n=125) (p=0.022). In both cohorts, DIA patients were significantly older than patients with UA. Interestingly, sBT levels were significantly higher in DIA patients compared to VIA in the Belgian cohort. Nevertheless, no statistically significant difference was found with regard to gender or total IgE levels (Table 4).

Furthermore, no significant differences were found when we conducted a subgroup analysis comparing mastocytosis with MMAS patients who developed DIA regarding clinical and demographic characteristics (Table E1, please see this article's Online Repository).

Additionally, we performed a comparative analysis with non-clonal patients who developed DIA to determine the presence of possible differences between the cohorts (Table 5). As anticipated, sBT levels were significantly higher among clonal patients. Moreover, in the Swedish cohort, clonal DIA patients were significantly older (considering age at diagnosis of mastocytosis) than non-clonal patients (p=0.017) (Table 5). Furthermore, the prevalence of DIA in mastocytosis patients was 2-fold higher (4%) compared to the DIA prevalence in non-clonal patients (2%) in the Swedish cohort, although that was not statistically significant. However, we could not compare the prevalence among clonal versus non-clonal Belgian patients, as non-clonal patients were exclusively referred due to suspected DHRs.

Discussion

This unprecedented study aimed at systematically investigating the prevalence and clinical characteristics of anaphylaxis to various drug classes in mastocytosis. To our knowledge, this is the largest study cohort investigating DIA among 470 adult mastocytosis patients enrolled in two reference centers.

The prevalence of DHR in the general population ranges from 0.7% to 23% with an estimated overall prevalence of 7.9% across the world (29,30). The discrepancies between studies may depend on using different definitions, heterogeneity in methodologies, variation in genetic predisposition, diverse geographical prescription patterns of drugs and participation rate across various age groups (1-3). However, studies reporting the prevalence of DIA in the general population are sparse. Our study shows that DIA occurs in approximately 6% of patients and counts for 1/3 of DHR in patients with mastocytosis. An Italian study investigating DIA among 94,073 cases seeking emergency care, reported a DIA prevalence of 0.6% (31). Another study found 1.2% of 2,148 adults visiting their general practitioners developed a DIA (32). Furthermore, an American study, conducted in tertiary health care centers, estimated a DIA prevalence of 1.1%, and reported a 4-fold higher risk of developing DIA in mastocytosis patients compared to the health care system population (6). Moreover, data from the Swedish cohort show that the prevalence of DIA in mastocytosis is a 2-fold higher than in patients without clonal disorders (although this was not statistically significant). Synthetically, all these observations point in the direction DIA to be more prevalent in mastocytosis. However, analysis of the European Anaphylaxis registry revealed that DIA accounted for 14% of severe anaphylaxis in adults from the general population (33). Interestingly, in our study, patients with DIA comprised 12.4% (30 of 242) of patients with history of anaphylaxis, whereas 59% (143 of 242) of anaphylaxis were caused by Hymenoptera stings. Hence, there is still an approximately 5-fold less risk compared to develop venom-induced anaphylaxis. Although, one could argue that the prevalence of DIA is low in our series likely as a result of overlooked anaphylaxis, the diagnosis of anaphylaxis was established in approximately half of all patients in both cohorts. This corresponds to the highest rate of anaphylaxis described in mastocytosis (12,13).

Another important finding relates to severity and clinical presentation of DIA in mastocytosis. A study on 125 non-clonal patients with DIA diagnosed in an allergy clinic showed a predominance of cutaneous symptoms, that were present in almost all subjects, followed by respiratory symptoms (3). Of note, cardiovascular symptoms accounted for less than half of the cases (3). Conversely, in both cohorts with mastocytosis cardiovascular symptoms were invariably present and almost half of the patients presented with hypotensive syncope. This is consistent with the previous reports, since such a specific clinical pattern of anaphylaxis was demonstrated in mastocytosis patients experiencing UA or VIA (14,34). This is most probably due to the inherent hyperreactivity of MCs in mastocytosis (10-13). Interestingly, in the current study, DIA was the clinical manifestation leading to the diagnosis of ISM only in two cases. It is important to note that cutaneous symptoms were frequent in DIA patients with mastocytosis; a clinical presentation that differs from the typical presentation of VIA in mastocytosis.

With regard to the culprits, NSAIDs were the most common elicitors of DIA accounting for more than half of the cases in our study. This is consistent with previous studies in the general population reporting NSAIDs as the most common culprit of DIA cases ranging from 43% to 72% (1,3). Moreover, the previous studies also reported that NSAIDs were the most common culprit causing DIA in

mastocytosis (34,35), although most mastocytosis patients tolerate NSAIDs (17,18). Perioperative anaphylaxis was responsible for one out of five cases of DIA and mainly involved rocuronium and atracurium. Our results are in line with the Spanish study (35). Remarkably, while antibiotics, especially β -lactams, constitute the most frequent triggers of DIA in the USA (66.5%), the UK (38%), Portugal (42%) (1-3), they were the third common culprits in this cohort by accounting for approximately 1 out of 10 DIA cases.

Alternatively, our data show that the prevalence of DIA due to so-called high-risk drugs that are frequently subjected to precautionary recommendations is rare. None of our patients experienced anaphylaxis to local anesthetics, except one who developed bupivacaine-induced anaphylaxis during spinal anesthesia. No DIA to RCM or vaccines were observed in our population. This is in line with other studies that show RCM and vaccines being uncommon triggers of anaphylaxis in adult patients with mastocytosis (36,37). In other words, these data argue against fear of using these drugs.

Skin tests/sIgE were useful as confirmatory tests in 5/30 patients. It is important to highlight that in 17/30 patients NSAIDs were the culprit and skin tests with these drugs are not reliable. Moreover, in 2/30 patients the interval between testing and DIA has probably influenced sensitivity of the tests. Finally, the patient with brentuximab induced anaphylaxis was not tested. All in all, we think that the allergy testing in patients with DIA and mastocytosis has the same performance than in patients without mastocytosis.

Our analysis on risk factors for DIA reveals that patients with DIA and mastocytosis were significantly older than patients with mastocytosis and anaphylaxis due to other causes as well as patients with DIA without mastocytosis, when considered their ages at diagnosis of mastocytosis. Older age, probably associated with a higher drug exposure, is reported as risk factor for developing anaphylaxis to drugs in the literature (1,3). Atopy has been reported to be a risk factor for developing anaphylaxis in mastocytosis (13,14). However, none of the DIA patients displayed atopy in our cohort. Contrary to previous reports, our study did not observe a significant difference in susceptibility between genders in developing DIA. Finally, MMAS patients exhibited a higher prevalence of DIA in both cohorts, especially in regard to perioperative anaphylaxis.

The main limitation of our study is its retrospective nature, potentially leading to recall bias resulting in a potential risk of over- or underdiagnoses of DIA. Furthermore, we acknowledge the absence of matching and stratification. As this study mainly based on comparisons analysis between the groups, it does not allow to make proper risk factor analyses with calculation of odds ratio, hazard ratio and risk ratio. Problems are compounded by the fact that confirmatory in vitro and in vivo diagnostics are lacking for most of the culprits and challenges to be excluded for obvious ethical reasons. Alternatively, the diagnosis of DIA was based on a thorough evaluation by a trained allergist and confirmed by significant increase in acute tryptase in 50% of the cases.

The main strengths of this study are the systematic investigation with a follow-up of approximately 7 years, the size of the cohorts, and its multicentric character. Actually, all participants underwent a comprehensive, individualized allergy workup with appropriate skin and/or in vitro tests, and if appropriate a DCT. This adds valuable information about the clinical characteristics, culprits and safe compounds in patients with mastocytosis and DIA. Moreover, unlike a transversal approach with analysis at a single predefined time-point, the longitudinal follow-up adds rigor to our observations.

This study includes a large population enrolled in two different centers, with overall a high prevalence of anaphylaxis. Interestingly, both centers had comparable findings.

In conclusion, although DIA tends to be higher in mastocytosis compared to the general population, its prevalence remains low and way below the prevalence of VIA in this specific population. Our results support the recommendation that mastocytosis patients with a prior reaction to drugs can benefit from a judicious allergy workup with identification of culprits and safe alternatives. Further use of tolerated drugs should not be dissuaded and does not necessitate specific precautionary measures. This study may serve as a start point for the development of paradigms that challenge the too generic avoidance and pretreatment advices regarding drug stewardship in systemic mastocytosis.

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AUTHOR CONTRIBUTIONS

M.B. collected and analyzed the data and took active part in interpreting the data as well as drafting the manuscript. V.S. took active part in the designing the study, analyzing and interpreting the data as well as drafting and revising of the manuscript. D.E. took active part in data interpretation and revised the manuscript critically. T.Z. collected and analyzed the data and took active part in interpreting the data as well as drafting the manuscript. T.G. conceptualized and designed the study; analyzed and interpreted the data; wrote and revised the manuscript; and supervised the project.

All authors approved the final submitted manuscript.

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Table 1. Demographics and characteristics of included subjects in both cohorts

	SWEDISH COHORT				BELGIAN COHORT			
Characteristics	SM (n=188)	MIS/CM (n=16)	MMAS (n=48)	Total (n=252)	SM (n=135)	MIS/CM (n=19)	MMAS (n=64)	Total (n=218)
Male gender, n (%)	86 (46.0)	6 (37.5)	25 (52.1)	117 (46.4)	55 (40.7)	6 (31.6)	35 (55.6)	96 (44)
Age (years) at diagnosis, median [range]	52 (18–84)	39 (18–76)	52 (28–74)	52 (18–84)	48 (18–86)	35 (18–64)	52 (18–81)	49 (18–86)
Baseline tryptase(ng/mL), median [range]	29 (6–650)	11 (3–160)	10 (3–31)	23 (3–650)	20.5 (3.9–707)	11.6 (3.1–88)	9.2 (4.3–66.6)	15 (3.1–707)
Total IgE (kU/L), median [range]	15 (1–1600)	13 (2–180)	42 (6–1100)	19 (1–1600)	25.5 (2–1189) (49 n/a)	41 (4–300) (6 n/a)	60 (6–1063) (13 n/a)	41 (2–1189) (68 n/a)
Presence of MC aggregates, n (%)	101 (55.8) (6 n/a)	0 (12 n/a)	0 (14 n/a)	101 (43.9) (32 n/a)	76 (56.2) (13 n/a)	0 (7 n/a)	0 (7 n/a)	76 (34.9) (27 n/a)
Presence of atypical morphology, n (%)	173 (96) (7 n/a)	0 (0) (12 n/a)	7 (20.6) (14 n/a)	180 (82.2) (33 n/a)	90 (66.6) (18 n/a)	0 (7 n/a)	9 (15.5) (6 n/a)	99 (45.4) (30 n/a)
Presence of CD25, n (%)	180 (100) (8 n/a)	2 (40) (11 n/a)	31 (88.6) (13 n/a)	213 (96.8) (32 n/a)	93 (68.9) (27 n/a)	0 (7 n/a)	34 (59.6) (7 n/a)	127 (71.8) (41 n/a)
Presence of D816V mutation, n (%)	146 (85.4) (17 n/a)	7 (50.0) (2 n/a)	23 (47.9)	176 (75.5) (19 n/a)	122 (90.3)	0 (0)	43 (67.2)	168 (77.1)
Presence of skin mastocytosis lesions, n (%)	114 (60.6)	16 (100)	0 (0)	130 (51.6)	85 (63)	19 (100)	13 (20.3)	117 (53.7)
Presence of atopy, n (%)	51 (27.4) (2 n/a)	4 (26.7) (1 n/a)	19 (40.4) (1 n/a)	74 (29.8) (4 n/a)	n/a	n/a	n/a	n/a
Presence of asthma and/or rhinitis, n (%)	45 (24.3) (3 n/a)	3 (20) (1 n/a)	19 (41.3) (2 n/a)	67 (27.2) (6 n/a)	n/a	n/a	n/a	n/a
History of any anaphylaxis, n (%)	97 (51.6)	2 (12.5)	36 (75.0)	135 (53.6)	61 (45.1)	1 (5.2)	45 (70.3)	107 (49.1)

Abbreviations: SM, systemic mastocytosis; MIS, mastocytosis in the skin; CM, cutaneous mastocytosis; MMAS, monoclonal mast cell activation syndrome; n/a: not applicable.

Table 2. Prevalence of drug-induced hypersensitivity and anaphylactic reactions among the study subjects.

Characteristics	Total	Mastocytosis	MMAS	p-value*
	(n=252)	(n=204)	(n=48)	
Overall drug-hypersensitivity, n (%)	58 (23)	47 (23)	11 (22.9)	ns
Overall drug-induced anaphylaxis, n (%)	10 (4.0)	7 (3.4%)	3 (6.3)	ns
NSAID-induced anaphylaxis, n (%)	5 (2.0)	4 (2.0)	1 (2.1)	ns
Perioperative drug-induced anaphylaxis, n (%)	3 (1.2)	1 (0.5)	2 (4.2)	ns
Antibiotic-induced anaphylaxis, n (%)	2 (0.8)	2 (1.0)	0 (0)	ns
	(n=218)	(n=154)	(n=64)	
Overall drug-hypersensitivity, n (%)	28 (12.8)	18 (11.7)	10 (15.6)	ns
Overall drug-induced anaphylaxis, n (%)	20 (9.1)	13 (8.4)	7 (10.9)	ns
NSAID-induced anaphylaxis, n (%)	12 (5.5)	9 (5.8)	3 (4.7)	ns
Perioperative drug-induced anaphylaxis, n (%)	4 (1.8)	1 (0.6)	3 (4.7)	0.043
Antibiotic-induced anaphylaxis, n (%)	2 (0.9)	1 (0.6)	1 (1.6)	ns
	(n=470)	(n=358)	(n=112)	
Overall drug-hypersensitivity, n (%)	86 (18.3)	65 (18.2)	21 (18.8)	ns
Overall drug-induced anaphylaxis, n (%)	30 (6.3)	20 (5.6)	10 (8.9)	ns
NSAID-induced anaphylaxis, n (%)	17 (3.6)	13 (3.6)	4 (3.6)	ns
Perioperative drug-induced anaphylaxis, n (%)	7 (1.5)	2 (0.6)	5 (4.5)	0.003
Antibiotic-induced anaphylaxis, n (%)	4 (0.9)	3 (0.8)	1 (0.9)	ns

*p-value (comparison mastocytosis vs MMAS) was calculated using the chi-square test or Fisher's exact test depending on sample size. MMAS, monoclonal mast cell activation syndrome; ns, non-significant; NSAID, non-steroidal anti-inflammatory drug. In the Belgian cohort, patients with DIA due to brentuximab and paracodeine are not shown here.

600 Table 3. Clinical characteristics of patients with drug-induced anaphylaxis.

Pt nr	Dx	Age at Dx	Total IgE (kU/L)	Culprit drug	SPT/IgE test/DCT	sBT (ng/mL)	Acute tryptase (ng/mL)	Clinical manifestations
1	ISM ⁻	72	270	Acetyl-salicylate	n/a	37	n/a	RESP, CARDV (syncope, hypotension), SKIN (urticaria)
2	MMAS ⁻	61	60	Acetyl-salicylate	n/a Neg DCT with meloxicam and etoricoxib	13.1	89.9	CARDV (hypotension), RESP (dyspnea), SKIN (flushing)
3 ^o	ISM ⁺	62	25	Amoxicillin-Clavulanic acid/ Acetyl-salicylate ^o	Neg testing to amoxicillin (Probably false negative because of long interval from index reaction) Neg DCT with etoricoxib	89.1	n/a	CARDV (hypotension), SKIN (erythema)
4	ISM ⁻	39	43	Diclofenac	n/a	13	58	CARDV (dizziness), RESP, SKIN (angioedema)
5	ISM ⁺	48	8	Diclofenac	n/a	34	n/a	CARDV (dizziness), Skin (pruritus), GI (abdominal pain, diarrhea)
6	ISM ⁻	61	22	Diclofenac	n/a	11	29	CARDV (syncope), SKIN (flushing)
7	MMAS ⁺	38	19.2	Diclofenac	n/a Neg DCT with celecoxib	19.6	n/a	CARDV (hypotension, syncope)
8	MMAS	66	96	Ibuprofen	n/a	21	n/a	RESP, CARDV (syncope, hypotension), SKIN (pruritus)
9	ISM ⁺	31	3	Ibuprofen	n/a Neg DCT with etoricoxib	200	n/a	CARDV (hypotension, syncope)
10	ISM ⁻	38	n/a	Ibuprofen	n/a Neg DCT with etoricoxib	80.7	201	CARDV (hypotension, syncope)
11	ISM ⁺	42	n/a	Ibuprofen	n/a Neg DCT with meloxicam	29.5	n/a	CARDV (hypotension)
12	MMAS ⁺	26	6.5	Ibuprofen	n/a Neg DCT with celecoxib	16.8	n/a	CARDV (hypotension, syncope), SKIN (flushing)
13	ISM ⁻	54	156	Ibuprofen	n/a Neg DCT with meloxicam	15.7	n/a	CARDV (hypotension, syncope), convulsions

14	ISM ⁻	61	67	Ibuprofen	n/a Neg DCT with celecoxib	17.3	125	CARDV (hypotension), SKIN (pruritus)
15	ISM ⁻	29	n/a	Ibuprofen	n/a Neg DCT with meloxicam	14.8	n/a	CARDV (hypotension), SKIN (pruritus)
16	ISM ⁻	53	454	Meloxicam	n/a Neg DCT with celecoxib	8.5	n/a	CARDV (hypotension), SKIN (pruritus)
17	ISM ⁺	51	n/a	Etoricoxib	n/a	19.3	n/a	CARDV (hypotension), GI (nausea), SKIN (hives)
18	MMAS ⁻	66	253	Rocuronium	IDT pos for Rocuronium, and IgE pos. for pholcodine	11.2	67.7	CARDV (hypotension), RESP (bronchospasm)
19	MMAS ⁻	77	53	Rocuronium	IgE pos for morphine; BAT rocuronium positive	25.4	201	RESP (bronchospasm)SKIN (angioedema, erythema)
20	ISM ⁻	32	6	Atracurium	Neg SPT/IDT tests with atracurium (in addition, suxamethonium and rocuronium IgE test neg)	63	190	CARDV (refractory hypotension), RESP (desaturation), SKIN (urticaria, angioedema)
21	MMAS	56	36	Atracurium	Neg SPT/IDT tests with atracurium (in addition, suxamethonium and rocuronium IgE test neg)	15	150	CARDV (refractory hypotension), RESP (desaturation)
22	MMAS ⁻	61	n/a	Heparin	Negative	20	101	RESP (bronchospasm) CARDV (cardio- respiratory arrest)
23	MMAS	74	35	Marcaine (spinal anesthesia)	Neg SPT	23	50	CARDV (hypotension), GI (nausea)
24	ISM ⁻	57	23	Unidentified culprit (lidocaine, chirocain, midazolam, sufentanyl, propofol, cefazolin, ondansetron)	All SPT/IDT neg.	65.2	201	CARDV (cardio-respiratory arrest)
25	MMAS ⁻	52	173	Amoxicillin-Clavulanic acid	Neg (Probably false neg because of long interval from index reaction)	8.9	n/a	CARDV (hypotension), RESP (dyspnea)

26	ISM ⁺	79	23	Penicillin V	Pos SPT to PCV	150	n/a	CARDV (dizziness, tachycardia), RESP (Dyspnea)
27	ISM ⁻	44	15	Penicillin V	Pos (PCV- IgE 0.26kU/L) Pos DCT	22	n/a	CARDV (syncope, hypotension), GI (nausea)
28	MIS	18	23	Paracodeine	n/a	6.7	n/a	CARDV (hypotension, syncope), GI (nausea)
29	SM-AHN (AML) ⁺	43	15	Brentuximab	n/a	326	1230	CARDV (hypotension, syncope), GI (nausea, vomiting)
30	ISM ⁻	65	256	Succinate (in methyl-predni-solone)	SPT pos to methyl-prednisolone succinate and hydro-cortisone succinate	44.8	63	CARDV (hypotension, syncope), RESP (dyspnea), SKIN (angioedema),

*Abbreviations: ISM, indolent systemic mastocytosis; MMAS, monoclonal mast cell activation syndrome; SPT, skin prick test; IDT, intradermal drug test; DCT, drug challenge test; PCV, penicillin V; BAT, basophil activation test; pos, positive; neg, negative; CARDV, cardiovascular; RESP, respiratory; GI, gastrointestinal.

Note: the +/- added to ISM indicates the presence of cutaneous lesions. ^o These were two separate episodes of anaphylaxis.

Table 4. Comparison of the mastocytosis patients with confirmed anaphylaxis based on the type of trigger.

	SWEDISH COHORT				BELGIAN COHORT			
Characteristics	DIA (n=10)	VIA (n=77)	UA (n=48)	<i>p-value</i>	DIA (n=20)	VIA (n=66)	UA (n=15)	<i>p-value</i>
Age (years) at diagnosis, median (range)	58.5 (32–79)	61 (22–80)	47 (18–70)	^a 0.001	52.5 (18–77)	55 (33–81)	46 (18–63)	^a 0.016
Male gender, n (%)	4 (40)	42 (59.2)	23 (51.1)	ns	12 (60.0)	32 (48.5)	9 (60.0)	ns
Baseline tryptase (ng/mL), median (range)	22.5 (11–150)	24.5 (7–110)	17 (3.1–160)	ns	19.5 (6.7–326)	11 (4.3 – 157)	13.6 (5–81)	^a 0.006
Total IgE (kU/L), median (range)	29 (5.5–270)	26.5 (2.6–1,000)	25 (3.1–1,600)	ns	56.5 (3–454)	47.5 (3.3–931)	51 (9–784)	ns
Presence of atopy, n (%)	0 (0)	17 (24.3) (1 n/a)	17 (39.5) (2 n/a)	^a 0.022	n/a	n/a	n/a	n/a
Presence of skin mastocytosis lesions, n (%)	2 (20)	42 (59.2)	13 (28.9)	ns	8 (40.0)	10 (15.2)	3 (20.0)	ns

Abbreviations: DIA, drug-induced anaphylaxis; VIA, venom-induced anaphylaxis; UA, unprovoked anaphylaxis; ns, non-significant; n/a, not applicable. ^ap-value was calculated using Kruskal-Wallis test. ^bp-value was calculated using Chi-square or Fishers exact test.

Table 5. Comparison between clonal and non-clonal patients who developed drug-induced anaphylaxis in our study population.

	SWEDISH COHORT			BELGIAN COHORT		
Characteristics	Cohort of study patients (n=252)	Non-clonal patients (n=397)	<i>p-value</i>	Cohort of study patients (n=218)	Patients with perioperative anaphylaxis (n=153)	<i>p-value</i>
Prevalence of DIA, n (%)	10 (4)	9 (2)	ns	20 (9.2)	153 (100)	n/a
Age (years) at diagnosis, median [range]	58.5 (32–79)	40 (25–68)	^a 0.017	52.5 (18–77)	52 (18–84)	ns
Male gender, n (%)	4 (40)	4 (44.4)	ns	12 (60)	56 (36.6)	ns
Baseline tryptase (ng/mL), median [range]	22.5 (11–150)	8.5 (2.7–23)	^a <0.001	19.5 (6.7–326)	4.81 (1.3–8.5)	^a <0.001
Total IgE (KU/L), median [range]	29 (5.5–270)	62 (14–2,200)	ns	56.5 (3–454)	95 (5.7–6,079)	ns
Presence of atopy, n (%)	0 (0)	3 (33.3)	^b 0.087	n/a	n/a	n/a
Presence of skin mastocytosis lesions, n (%)	2 (20)	0 (0)	ns	6 (0.3)	0 (0)	n/a

Note: ^ap-value was calculated using a two-tailed Mann-Whitney U-test. ^bp-value was calculated using Chi-square or Fishers exact test. Bold indicates statistical significance (P<0.05). ns, non-significant; n/a, not applicable.

FIGURE LEGENDS

Figure 1. Flow chart illustrating study population and selection process of study subjects.

Figure 2 – This figure illustrates the most common causes of drug-induced anaphylaxis in both cohorts, grouped per category of drugs. In bracket is the absolute number of patients in the Swedish and Belgian cohort, respectively. Other drugs consist of succinate, brentuximab and paracodeine.



