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A Multicenter retrospective study on hypersensitivity reactions to Non-Steroidal Anti-inflammatory Drugs (NSAIDs) in children: a report from the European Network on Drug Allergy (ENDA) group

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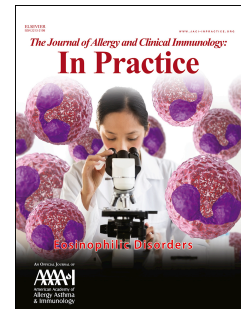
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A Multicenter retrospective study on hypersensitivity reactions to Non-Steroidal Anti-inflammatory Drugs (NSAIDs) in children: a report from the European Network on Drug Allergy (ENDA) group

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Abstract

Background: Diagnosis of hypersensitivity (HS) reactions to non-steroidal anti-inflammatory drugs (NSAIDs) in children is complex. The real prevalence of NSAIDs HS remains unknown because a drug provocation test (DPT) is not always performed with the culprit NSAID.

Objective: To describe and compare the diagnostic workup among different European centers and to find out the real proportion of NSAIDs HS by performing a DPT with the culprit drug.

Methods: We retrospectively collected data from children (0-10 years) and adolescents (10-18 years) with a history of NSAIDs reactions and who underwent a complete allergy workup including DPTs with the culprit in six different pediatric centers: Belgrade, Florence, Geneva, Madrid, Porto, and Rome.

Results: A total of 693 children with a history of NSAIDs reactions were enrolled and a total of 526 DPTs were performed with the culprit NSAID. The diagnosis of NSAIDs HS was confirmed in (103/526) 19.6% of children by performing a DPT with the culprit drug. The major differences in the allergy workup among the six centers concerned the duration of the DPT and the practical use of skin tests for diagnosing NSAIDs HS. In addition, the use of acetyl salicylic acid (ASA) to differentiate single reactors (SR) or cross-intolerance (CI) patients is not commonly used except in Spain.

Conclusion: The value of this study is that although different approaches are used around Europe to diagnose NSAIDs HS, we found that the percentage of confirmed NSAIDs HS is less than 20%. This highlights the importance of the DPT in confirming or excluding NSAIDs HS in the pediatric population.

Highlights box:**What is already known about this topic?**

Diagnosis of NSAIDs and paracetamol HS is complex and the exact prevalence remains unknown.

What does this article add to our knowledge?

To our knowledge this is the first multi-center study to evaluate a large number of pediatric/adolescent patients from different European centers with suspected NSAID/paracetamol HS.

How does this study impact current management guidelines?

This study highlights the importance of the DPT with the culprit NSAID/paracetamol in the allergy workup, showing that one-day DPT is commonly sufficient to reach a confident diagnosis

Key words:

Acetyl Salicylic Acid; Aspirin; Adolescents; allergy workup; Children; Drug Provocation tests; Ibuprofen; Hypersensitivity; Non-Steroidal Anti-Inflammatory drugs; Paracetamol

Abbreviations:

NSAIDs= Non-Steroidal Anti-Inflammatory drugs

HS= hypersensitivity

DPT= drug provocation test

SR= Selective Reactors

CI= cross-intolerance

ASA= Acetyl Salicylic Acid

COX= Cyclooxygenase

WHO= World Health Organization

IL= Interleukin

LTC= cysteinyl leukotriene

Introduction

Non-Steroidal Anti-Inflammatory drugs (NSAIDs) and paracetamol are commonly used in children, mainly as antipyretic, analgesic and/or NSAIDs as anti-inflammatory drugs. Of note, paracetamol (acetaminophen) is not a classic NSAID. However, due to its minor anti-inflammatory activity and its side effects profile extremely similar to that of NSAID from an allergic point of view, it is usually included as a NSAID.¹ Although NSAIDs have generally been shown to be safe, hypersensitivity (HS) reactions may occur.² Some studies have shown that the prevalence of NSAID HS is comparable or even greater than that reported for betalactam (BL) antibiotics HS.^{3,4} However, the exact prevalence remains unknown, as most of the studies are based on the clinical history, and a complete allergy workup to confirm or exclude a real allergy is lacking. Diagnosis of NSAID HS is difficult, mainly due to the lack of tests outside the drug provocation test (DPT) with a good diagnostic value, but also due to the limited knowledge of primary care physicians regarding drug allergy and the fear of severe reactions during the allergy workup. This often leads to an overdiagnosis. In the pediatric population, this problem is aggravated by the frequent presence of co-factors that are not well identified or absent at the time of the allergy workup or other agents such as viral infections that can mimic clinical manifestations of drug allergy. Moreover, knowledge regarding the age-related drug metabolism and its influence on NSAID HS is limited, and worldwide comparable epidemiological data are still lacking. Most of the data published on children comes from case reports and small series, and they are therefore subjected to biases, with only a few studies verified by DPT.⁵ For the adolescent age group, in most cases, they are included in large series where adults are also enrolled and frequently less than 20% of the patients are younger than 20 years old.⁴

Due to the limited number of pediatric studies, the proportion of real NSAID HS in children developing allergic symptoms while receiving this type of drug is not well-known, but appears to range from 2.5% to 92% depending on the type of reaction and the age of patients included.⁶⁻¹⁰

The complexity of the diagnosis and management of children with suspected NSAID HS is increased by the different entities of NSAID HS, as they can be due to specific immunological mechanisms [Selective Reactors, (SR)] or related to non-immunological mechanisms where the prostaglandin-leukotriene pathway could be the main route involved in these reactions, although other lipid inflammatory pathways could also participate to the arachidonic acid metabolism [non-allergic hypersensitivity or cross-intolerance [CI] reactions].¹¹ Even though it has been suggested that CI appears to be more common compared to SR HS in children,⁵ there is a lack of pediatric data regarding the frequency of the different phenotypes of reaction based on large studies. Furthermore, NSAID HS exhibits different specific characteristics in the pediatric group and the initial classification proposed by the EAACI/ENDA group do not fit properly with this age group.^{5,12-14} According to the new consensus proposed by the EAACI/ENDA group¹, adolescents can fit in the previous classification because the observed clinical pattern is similar to that of adults, with more anaphylaxis and challenge-proven diagnoses.^{15,16} Recently, several reviews summarized the available pediatric data.^{11,13,17,18} However a unified approach in children as well as a general agreement about guidelines are still lacking and the DPT, considered the gold standard for the diagnosis of NSAIDs HS,^{19,20} is not always performed.

The main objectives of this study were: a) to identify similarities and differences in the diagnostic workup among different centers in Europe; b) to compare the frequency of phenotypes and clinical manifestations observed in each country; c) to describe the NSAIDs including paracetamol most commonly reported as involved in drug HS reactions; d) to find out the real proportion of NSAID HS among children and adolescents by performing a DPT with the culprit drug.

Methods

We retrospectively collected data from children (0-10 years) and adolescents (10-18 years) with a positive history of NSAID reactions who underwent a complete allergy workup in six different

pediatric centers: Belgrade (Serbia), Florence (Italy), Geneva (Switzerland), Madrid (Spain), Porto (Portugal), and Rome (Italy). The periods of enrolment were: Belgrade 10 years (2006-2016), Florence 3 years (2013-2015), Geneva 8 years and 5 months (2008-2016), Madrid 4 years (2012-2015), Porto 4 years (2012-2016), and Rome 3 years (2014-2016). Children were classified as those with history of reaction to a single NSAID and those with history of reactions to multiple NSAIDs, these cases being either SR or CI patients after provocation with Acetyl Salicylic Acid (ASA).

In order to confirm or exclude the diagnosis of NSAID HS, an oral DPT was performed initially with the culprit drug or a strong cyclooxygenase (COX)-1 inhibitor (Spain). Most ASA challenges occurred in Madrid, but some were performed in all other centers except Geneva.

In case of severe initial reactions, a highly suggestive clinical history, or the parents' refusal, an alternative NSAID was tested with the DPT.

Because of the higher number of SR in Belgrade, skin tests were parts of the allergy workup as well as in Madrid (in the latter only to evaluate SR directly related to metamizole), but not in the other centers. The concentrations and formulations of NSAIDs tested for skin and intradermal testing are those summarized in the recent consensus paper by the EAACI/ENDA group.¹

The DPT was performed by oral route with two to four escalating doses of the drug, till a total dose adjusted by the body weight and patient's age every 30 to 90 minutes on the first day in a hospital setting (Table I) with available emergency facilities and trained personnel in order to promptly treat any possible reaction. In all the centers participating in the study, the period of observation after the drug administration was up to 3 hours after the last dose. The total length of the DPT differed in the recruiting centers: 4 centers did a 1 day-DPT with escalating doses, while 2 other centers did a 2- or a 3-day DPT (Madrid and Belgrade, respectively). (Table I).

A DPT was considered positive based on the appearance of any objective parameters: skin involvement (urticaria, exanthema), angioedema, respiratory symptoms (cough, conjunctivitis and

rhinitis, asthma, bronchospasm, hoarseness), gastrointestinal symptoms (vomiting, diarrhoea), hypothermia, loss of consciousness, tachycardia.

The results of the allergy workup were analyzed separately according to age: from childhood (0-10 years) and adolescence (10-18 years), considering both as the pediatric population. According to the World Health Organization (WHO) statements, the childhood range is up to 10 years old and the adolescence covers the ages from 10 to 19 years.²¹

Statistical analysis

The differences for the quantitative data were assessed by the Student's t test, and the differences for the qualitative data were assessed by the Chi² test or by Fisher's test when the number of cases was low. A p value < 0.05 was considered significant.

RESULTS

Characteristics of the patients enrolled

A total of 693 children with a history of NSAIDs HS reactions were enrolled. The demographic and clinical characteristics are summarized in Table II. The mean age ranges between 6 and 10 years, and no significant differences were observed in the gender. The percentage of multiple NSAID reactors were variable among centers. The majority of these patients did not have atopy [29.3% (n=203/693) of patients]; asthma 9.5% (n= 66/693) of patients] or urticaria 5.9% (n=41/693) of patients]. When focusing on the prevalence of atopy, asthma and urticaria according to age, no significant differences were found between children younger and those older than 10 years (Table II).

The clinical characteristics of the initial reactions to NSAIDs reported by the patients are listed in Table III. The reported reactions were mainly cutaneous reactions (707/814, 86.9%), in particular angioedema and/or urticaria were described. Of the remaining 107 reactions symptoms are described in Table III and the culprit drugs were Ibuprofen in 71 cases, paracetamol in 23 cases, ketoprofen in 3 cases, ASA in 3 cases, dexketoprofene in 2 cases, flurbiprofen in 2 cases, niflumic acid in one case, metamizole in one case, etoricoxib in one case.

Most of them (n=545/814, 66.9%) were within the first 6 hours after taking the NSAID and involved only the skin: i.e. urticaria and/or angioedema followed by respiratory tract (n=73/814, 8.9%), with a total of 70/814 (8.6%) systemic reactions (i.e. more than one system involved). Forty-three out of 70 (61.4%) systemic reactions occurred in children younger than 10 years and 27 out of 70 (38.6%) in the group older than 10 years (p= 0.44).

NSAID involved

The most frequently involved NSAID in all cases was ibuprofen except in Rome where the most frequently reported trigger provoking HS reactions was paracetamol (Figure I, Figure E1).

211 It is important to mention that not all NSAIDs were used in all centers. For example,
212 dipyrrone/metamizole, was only used in Belgrade, Madrid and Rome, while mefenamic acid only in
213 Geneva.

214 Regarding a potential influence of the age, we found that 112/693 (16.2%) children were younger
215 than 2 years and the most frequently suspected drug was ibuprofen both in those with a history of
216 reactions to a single NSAID (95/112=84.8%) and those with a history of reactions to different
217 NSAIDs (17/112=15.2%). In children younger than 6 years (305/693=44%), ibuprofen was also the
218 most frequently involved NSAID in all the centers participating in the study except for Rome where
219 paracetamol was on the top.

220

221 **Proportion of confirmed hypersensitivity**

222 In this study, a total of 526 DPTs were performed with the culprit NSAIDs. Seventy DPT were not
223 performed because of suggestive clinical history or history of severe reactions, and 97 refused DPT
224 because an alternative NSAID or paracetamol was tolerated or because of fear of the DPT. When
225 analyzing the cumulative results without a 'by-age' classification, the diagnosis of NSAID HS was
226 confirmed in 103/526 (19.6%) of the cases. Of note, the proportion of positive DPT was similar for
227 patients with paracetamol as culprit (25/129, 19.4%) and those with NSAID as culprit (78/397,
228 19.8%) ($p=0.95$). There were 85/444 (19.1%) positive DPTs in the group of children with history
229 of reaction to a single NSAID and 18/82 (21.9 %) belonging to the group of children with history of
230 reaction to multiple NSAIDs.

231 When analyzing patients with history of reactions to a single NSAID, the DPT with the culprit was
232 positive in 16.2% (50 out of 308) of patients aged 10 years or younger. In a group of very young
233 children (less than 2 years), the DPT with the culprit confirmed the diagnosis in only 7 out of 94
234 DPTs (7.4%). Children older than 10 years had a positive DPT with the culprit in 26% cases (35 out
235 of 136). When patients with history of reaction to a single NSAID were tested with alternative
236 NSAIDs, 31.6% of children below 10 years (19 out of 60) and 52.2% (24 out of 46) of children

237 over 10 years were positive (Figure II) (culprit $p=0.02$; alternative $p=0.03$). The same proportion of
238 positive DPTs with an alternative NSAID was observed in children with history of reactions to
239 more than one NSAIDs (18.8% of children between 0-10 years vs. 44.4% of children over 10 years)
240 ($p=0.16$). Most centers used an alternative on-label antipyretic/analgesic with low COX-1 activity
241 without a specific preference.

242 ASA was tested as an alternative NSAID in 159 out of a total of 693 patients (22.9%). Forty-three
243 out of 159 (27%) children were positive: 18 younger than 10 years (11 out of 18 with atopy) and
244 25 over 10 years (20 out of 25 with atopy). It should be noted that 145 out of a total of 159 of these
245 DPTs with ASA were performed in Spain where ASA was tested instead of culprit being a strong
246 COX-1 inhibitor. In this group of patients, atopy seems to be more prevalent in those children, both
247 younger and older than 10 years, who reacted to ASA. Of the remaining 14 DPTs with ASA, 5 were
248 performed in Rome, 4 in Florence, 4 in Belgrade, 1 in Porto, and none in Geneva.

249 Ibuprofen is the NSAID most frequently confirmed as responsible for a true state of HS (Figure I,
250 Figure E1). Those children with a confirmed HS to NSAIDs were not more atopic than those in
251 which NSAID HS was ruled out.

252 In detail, among the 103 children with a positive DPT to the culprit, 63 were ≤ 10 years and 40
253 were older than 10 years. Only 16 out of 63 (25.4%) younger children were atopic and only 9 out of
254 40 (22.5%) adolescents were atopic, with no significant statistical differences between the two age
255 groups ($p=0.7$).

256 Regarding the type of reactions to the DPT most of them were cutaneous reactions or isolated
257 angioedema (90%) and also when systemic reactions were confirmed (7% of cases) those were not
258 severe neither required hospitalization.

259 In more detail, isolated facial angioedema, especially when localized on lips or eyelids, is more
260 prevalent in children with a history of reactions to multiple NSAIDs (68/119=80.9%) and in older
261 children in particular in 128/234 (54.7%) over the age of 10 and in 187/459 (40.7%) under the age
262 of 10 ($p=0.0005$). Systemic reactions in the acute phase of an infectious disease tended to occur

263 more frequently in younger children 61.4% (43/70) vs. 38.6% (27/70) of the adolescents, although
264 the difference did not reach statistical significance ($p=0.44$).

265

Discussion

Although NSAIDs are generally well tolerated in children, together with BLs they are the most frequent suspected cause of HS reactions. According to literature, more children claim to be allergic to BLs but only <10% can be confirmed after completing the allergy workup.^{19,22} On the contrary, studies on NSAIDs show that NSAID HS is confirmed more frequently. Nevertheless, the prevalence of proven NSAID HS varies greatly among studies depending on whether it has been proven by DPTs or only based on the clinical history. In more recent studies, children and adolescents with a suspected history of NSAID-induced HS reaction have been challenged with the culprit drug, with a prevalence of NSAIDs assessed at around 20-25% (8-68%) in different populations.^{5,7,9,14,16,17,23-27} To our knowledge, this is the largest study published so far including only patients younger than 18 years with a percentage of confirmed NSAID HS of 19.6% based on 526 DPTs performed with the culprit NSAID or a stronger one. This result underlines the importance of performing DPTs with the culprit (or strong COX-1 inhibitors) in order to avoid a mislabeling of patients as hypersensitive to NSAIDs, even though challenging with the culprit alone does not enable a better phenotyping of patients. Of note, if we consider “allergic” also the 70 children with a suggestive clinical history of severe reactions (not challenged) as well as the 20% of those who refused a DPT with the culprit, the percentage of confirmed NSAID HS is in the same range (29% (202/693 children)).

In our study, the most frequent NSAIDs triggers of HS reactions were ibuprofen (66/103 64%) and paracetamol (24/103 23.3%), with the last one being only reported as the main elicitor in Rome. Comparing this result to other published in the literature we found that Kidon et al.²⁸ also reported paracetamol HS as more common among children younger than 6 years of age. Zambonino et al.²⁴ found ASA to be the second most common agent and paracetamol was reported as the drug encountered most infrequently. The differences observed in our study among the centers participating in terms of the NSAIDs involved may reflect variations in the

consumption/prescription patterns, the epigenetic differences of the population studied, and the range time when the patients were enrolled.

In pediatrics, influence of the age on the immune system but also on the rate of viral infection is well known. In order to evaluate a potential influence of the age on the rate of confirmed NSAID HS, the patients were divided in 2 different groups, those younger than 10 years of age and those older. We found that the DPT is even more important in younger children (≤ 2 years) where the diagnosis is confirmed only in the 7% of patients evaluated. In fact, in agreement with literature, we confirmed NSAID HS in a higher percentage of patients over 10 years ($n=72/228$) than in children equal or under the age of 10 ($n=84/433$) ($p=0.0005$). A possible explanation already proposed in the previous studies, could be that in younger children the role of probable concomitant viral infections has to be taken into account when investigating NSAID reactions, because we can hypothesize that skin rashes (i.e. acute urticaria) due to viral infection more commonly occur in younger children than in older, possibly mimicking drug allergy.²⁹

The clinical pattern of reactions reflects those reported in literature with a predominance of angioedema with or without urticaria. Moreover, our results confirm data of other studies published where the skin (either isolated or combined with respiratory symptoms) is the most frequent organ involved in NSAID reactions. The pattern of reactions, either mediated by specific or other immunological mechanisms, may also have differentiated age-related clinical characteristics. Systemic reactions in the acute phase of an infectious disease tended to occur more frequently in younger children. This is not in agreement with literature where systemic reactions are more common in adolescent.³² A possible explanation is the fact that the number of children ≤ 10 years included in this study is double the number of adolescents (Figure II), which might affect the results. Moreover, this value could be overestimated by concomitant viral diseases with respiratory or gastrointestinal symptoms. Of note, systemic reactions were rarely confirmed during the DPTs

(7%). Most of the reactions occurred during DPTs were cutaneous reactions or isolated angioedema.

In this study, atopy affected about 35-40% of children with a suspicion of NSAID HS (comparable to the percentage in the general population 40-50%)³³, except for the Serbian children where atopy was less frequent (8%). According to our results and data in literature,²⁴ the prevalence of atopy was higher in the group of patients with reactions to the alternative drug or to ASA, mainly in the Madrid center (61.1% ≤ 10 years and 80% > 10 years). In our study, the percentage of atopy in patients with confirmed NSAID HS is 38% (n=56/146) compared to the 17.6% (= 94/535) observed in the negative group (p<0.0001).

Regarding the practical approach to diagnose HS to NSAID, the majority of the centers start with the DPT with the culprit NSAID, with an observation time of 2-3 hours after the final dose administered. Most of the centers start with 1/10 of the dose, except in Rome where the first dose administered was higher (1/4 of the total dose). As far as the length is concerned, most centers only challenge for one day in a hospital setting, except for Madrid (2 days) and Belgrade (3 days, the two last days at home). In Madrid all except for 3% reacted the first day, with a time interval of 4-6 hours after the last dose administered. In Belgrade, 50% reacted on the first day, approximately 30% on the second day, and 20% on the third day as previously shown. Finally, another difference observed concerned the DPT with ASA, which is mainly performed in Madrid with very few ASA DPTs performed in the other centers participating (145/148 in Madrid vs. 14/513 in the other centers). In Madrid 35/145 (24%) were CI patients. Anyhow, whatever the approach, approximately the same proportion of patients are confirmed, and the main purpose of the allergy workup for the drug allergy is mainly to exclude a severe allergy. Thus, our data suggest that a single day is probably appropriate. Of note, the lack of blinded DPT in the vast majority of our patients might lead to an overestimation of the proportion of confirmed hypersensitivity due to false positive DPT. This reinforces our main message which is that we should challenge with the culprit NSAID as only a small percentage (less than 19.6%) will have a confirmed NSAID hypersensitivity.

The data presented in this study show how children evaluated with NSAID HS react to the alternative drug and therefore are highly likely to be CI patients. In any case, it must be noted that when the alternative NSAID was not ASA, the proportion of CI could be underestimated. Several authors highlight the importance of a DPT to ASA for a correct classification (CI versus selective reactors), as it is the strongest cox-1 inhibitor. However, some concerns exist regarding side effects of ASA, particularly the Reye's syndrome, when considering the administration of ASA in children. In consequence, most patients included in this study cannot be classified due to the lack of DPT to ASA. This reflects real clinical practice and shows that most pediatric allergists in Europe do not usually aim to classify their patients. Their objective is mainly to confirm or exclude a hypersensitivity by challenging with the culprit drug and then testing an alternative, mainly paracetamol. This attitude limits the number of DPTs, which are time consuming and associated with high medical costs. Drawbacks of this approach is that non-tested NSAIDs should be avoided in case of confirmed NSAID hypersensitivity. This important point of the study highlights differences and variability of clinical practice in children with a suspicion of NSAID hypersensitivity children throughout Europe.

Another difference observed in the management was the use of the skin test as part of the diagnostic workup in Belgrade. Nevertheless, skin tests with NSAIDs were negative in 70.6% of cases (in particular in 30 patients with negative SPTs and positive DPTs), confirming poor performance in this clinical setting especially in the case of CI patients.⁷ Moreover, there could be a high chance of false positive as it is already known the poor performance of skin tests with NSAIDs drugs;²³ those patients have not been challenged and the percentage of confirmed NSAID HS based on this might explain the higher percentage found in Belgrade. In the other centers children were provoked without previous skin tests and had no severe reactions. More studies evaluating the negative and positive predictive values of skin tests in comparison with DPT results should be performed, in

order to give recommendations of skin test diagnostic efficacy in the allergy work-up of NSAIDs reactions.

The limitation of our study was that it was a retrospective investigation based on clinical chart reviews. Based on a large number of patients, this study provides major information regarding the clinical characteristic of patients with suspicion of NSAID HS at different ages. The value of this study is that even though different approaches are used around Europe to diagnose NSAID HS, we found that the percentage of confirmed NSAID HS is less than 20%. This highlights the importance of DPTs in the pediatric population for confirming or ruling out NSAID HS.

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Figures legends

FIGURE I. Culprit NSAID in different centres according to both clinical history and DPT results.

a) Clinical history of reaction to **single** NSAID (absolute number); positive DPT to culprit drug on total of DPTs performed. b) Clinical history of reaction to **multiple** NSAIDs (absolute number); positive DPT to one of the culprit drug on total of children tested c) cumulative data

FIGURE II. Diagnostic flow chart of 693 patients with suspected NSAID hypersensitivity.

TABLE I. Open DPT with the culprit/alternative NSAID among different centers.

	Belgrade	Florence	Madrid	Geneva	Porto	Rome
DPT Protocol: up-dosing intakes of the culprit/alternative drug (1/100 or 1/10-2/10-7/10) every 30-90 minutes for the 1° day in hospital setting	X	X	X	X	X	$\frac{1}{4} + \frac{3}{4}$ of dose 1/100, 1/10 and full dose in cases of anaphylaxis
Time of observation: 2-3 hours	X	X	X	X	X	X
1-day DPT		X		X	X	X
2-day DPT (on the second day the entire dose was administered in the hospital either all at once or in two doses)			X * (3% reacted the second day)			
3-day DPT	X ("at home" drug intake after the first day) *(30% reacted the second day and 20% reacted the					

	third day)					
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TABLE II. Clinical and demographic characteristics

Hospitals	Number of patients	Sex (M:F)	Mean Age (range)	Multiple NSAIDs reaction	Personal Atopy			Asthma			Chronic or recurrent Urticaria	
Belgrade (Serbia)	196	93:103	9,07 yrs (10 mo-18 yrs)	20 (10,2%)	16 P (8,2%)	180 N (91,8%)	0 NK (0%)	2 P (1%)	194 N (99%)	0 NK (0%)	19 P (9,7%)	177 N (90,3%)
Florence (Italy)	152	69:83	7,22 yrs (2 mo-18 yrs)	45 (29,6%)	50 P (32,9%)	102 N (67,1%)	0 NK (0%)	11 P (7,2%)	141 N (92,8%)	0 NK (0%)	10 P (6,6%)	142 N (93,4%)
Geneva (Switzerland)	95	40:55	6,33 yrs (6 mo-18yrs)	20 (21%)	38 P (40%)	40 N (42%)	17 NK (18%)	7 P (7,3%)	71 N (74,7%)	17 NK (18%)	8 P (8,4%)	87 N (91,6%)
Madrid (Spain)	148	81:67	9,04 yrs (7 mo-18yrs)	12 (8,1%)	60 P (40,6%)	20 N (13,5 %)	68 NK (45,9%)	24 P (16,2%)	124 N (83,8%)	0 NK (0%)	-	-
Porto (Portugal)	52	28:24	6,9 yrs (12 mo-17 yrs)	3 (5,8%)	19 P (36,5%)	33 N (63,5)	0 NK (0%)	19 P (36,5%)	33 N (63,5)	0 NK (0%)	4 P (7,7%)	48 N (92,3%)
Rome (Italy)	50	25:25	10,68 yrs (12mo-16 yrs)	19 (38%)	20 P (40%)	30 N (60%)	0 NK (0%)	3 P (6%)	47 N (94%)	0 NK (0%)	-	-
Total	693	336:357	-	119 (17,2%)	203P* (29,3%)	405 N (58,4%)	85 NK (12,3%)	66P** (9,5%)	610N (88%)	17NK (2,5%)	41 P*** (5,9%)	454N (65,5%)

Note: Yrs: years; mo: months.

P: positive; N: negative; NK: not known

* 203 with Atopy:

- ≤ 10 yrs: 115/203 (56,7%)
- > 10 yrs: 88/203 (43,3%)

** 66 with Asthma:

- ≤ 10 yrs: 36/66(54,6%)
- > 10 yrs: 30/66(45,4 %)

*** 41 with Urticaria:

- ≤ 10 yrs: 24/41(58,5%)
- > 10 yrs: 17/41(41,5%)

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Symptoms	Latency of reactions	Belgrade (Serbia) NoR: 218	Florence (Italy) NoR: 202	Geneva (Switzerland) NoR: 117	Madrid (Spain) NoR: 159	Porto (Portugal) NoR: 55	Rome (Italy) NoR: 63	Total NoR: 814		
Isolated urticarial and/or angioedema	≤ 1h	-	55	23	67	-	-	145	Only skin involvement (707/814, 86,8%)	
	From 2 to 6h	143	31	17	47	-	55	293		
	> 6h	71	28	8	9	-	5	121		
	<24 h°	-	-	-	-	11	-	11		
	>24h°	-	-	-	-	7	-	7		
	Unspecified	-	20	13	3	-	-	36		
	Total n (%)	214 (98,2%)	134 (66,3%)	61 (52,1%)	126 (79,3%)	18 (32,7%)	60 (95,2%)	613		
Other isolated cutaneous symptoms (Itchy rash, maculopapular exanthema, erythema, bullous rash)	≤ 1h	-	12	2	3	-	-	17		
	From 2 to 6h	-	10	3	5	-	-	18		
	> 6h	1	9	13	8	-	-	31		
	<24 h°	-	-	-	-	5	-	5		
	>24h°	-	-	-	-	10	-	10		
	Unspecified	-	10	3	-	-	-	13		
	Total n (%)	1 (0,4%)	41 (20,3%)	21 (17,9%)	16 (10%)	15 (27,3%)	0 (0%)	94		
Respiratory symptoms (cough, conjunctivitis and rhinitis, asthma, bronchospasm, hoarseness)	≤ 1h	-	-	2	2	-	-	4	Other organs involvement (107/814, 13,2%)	
	From 2 to 6h	-	-	3	-	-	-	3		
	<24 h°	-	-	-	-	5	-	5		
	>24h°	-	-	-	-	4	-	4		
	Total n (%)	0 (0%)	0 (0%)	5 (4,3%)	2 (1,3%)	9 (16,3%)	0 (0%)	16		
GI symptoms (vomiting, abdominal pain, diarrhoea)	≤ 1h	-	1	-	-	-	-	1		
	Unspecified	-	1	-	-	-	-	1		
	Total n (%)	0 (0%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2		
Cutaneous + GI symptoms	≤ 1h	-	2	2	-	-	-	4		
	From 2 to 6h	-	-	1	-	-	-	1		
	> 6h	-	-	1	-	-	-	1		
	<24 h°	-	-	-	-	2	-	2		
	>24h°	-	-	-	-	1	-	1		

	Unspecified	-	1	1	-	-	-	2
	Total n (%)	0 (0%)	3 (1,5%)	5 (4,3%)	0 (0%)	3 (5,5%)	0 (0%)	11
Cutaneous + Respiratory symptoms	≤ 1h	-	8	9	14	-	2	33
	From 2 to 6h	2	-	2	1	-	-	5
	> 6h	-	-	2	-	-	-	2
	<24 h°	-	-	-	-	7	-	7
	Unspecified	-	-	2	-	-	-	2
	Total n (%)	2 (1%)	8 (4%)	15 (12,8%)	15 (9,4%)	7 (12,7%)	2 (3,2%)	49
GI + Respiratory symptoms	≤ 1h	-	-	2	-	-	-	2
	>24h°	-	-	-	-	1	-	1
	Total n (%)	0 (0%)	0 (0%)	2 (1,7%)	0 (0%)	1 (1,8%)	0 (0%)	3
GI + Respiratory + Cutaneous symptoms	≤ 1h	-	-	4	-	-	-	4
	>24h°	-	-	-	-	1	-	1
	Total n (%)	0 (0%)	0 (0%)	4 (3,4%)	0 (0%)	1 (1,8%)	0 (0%)	5
Anaphylactic shock[^]	≤ 1h	-	1	-	-	-	1	2
	Total n (%)	0 (0%)	1 (0,5%)	0 (0%)	0 (0%)	0 (0%)	1 (1,6%)	2
Other symptoms (lipotomies, hypothermia, joint swelling, pallor)	≤ 1h	1	5	1	-	-	-	7
	From 2 to 6h	-	4	2	-	-	-	6
	> 6h	-	2	-	-	-	-	2
	>24h°	-	-	-	-	1	-	1
	Unspecified	-	2	1	-	-	-	3
	Total n (%)	1 (0,4%)	13 (6,4%)	4 (3,4%)	0 (0%)	1 (1,8%)	0 (0%)	19

H: hours

° In the Serbian population *acute reaction* mean < of 12-24 hours and *delayed reaction* mean more than 12-24 hours.

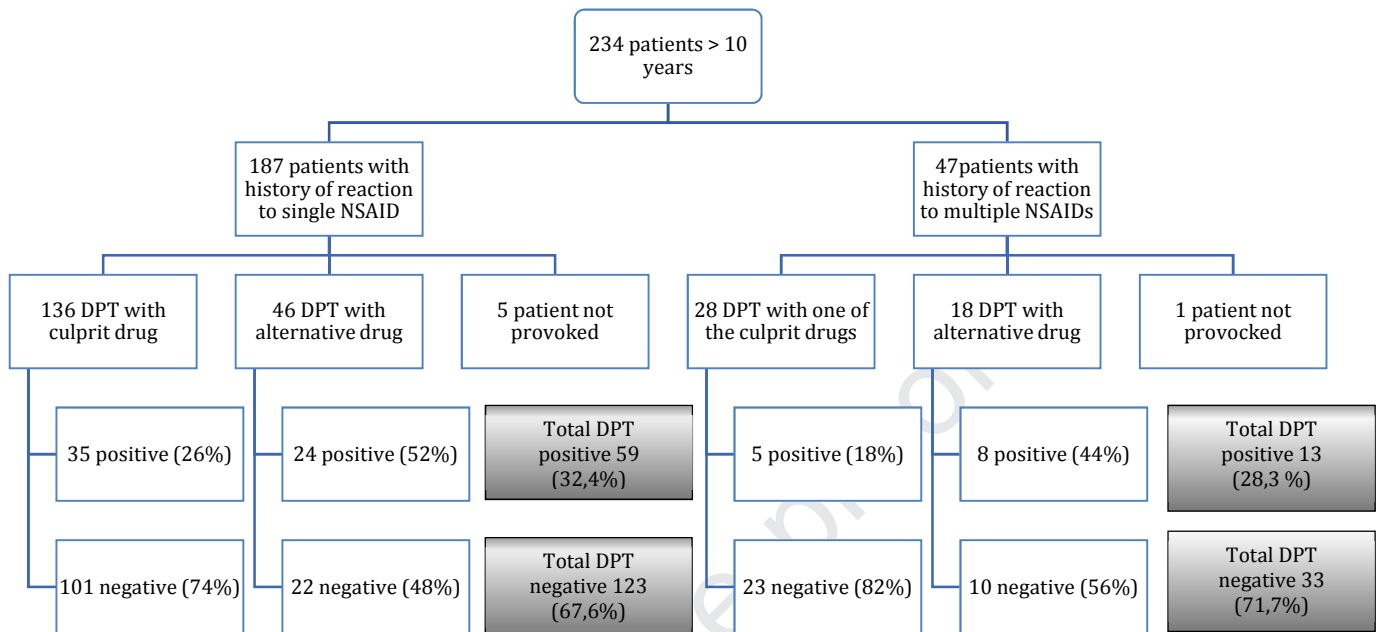
[^] Gastrointestinal symptoms and/or cutaneous symptoms and/or respiratory symptoms AND hypotension or loss of consciousness

GI: Gastrointestinal

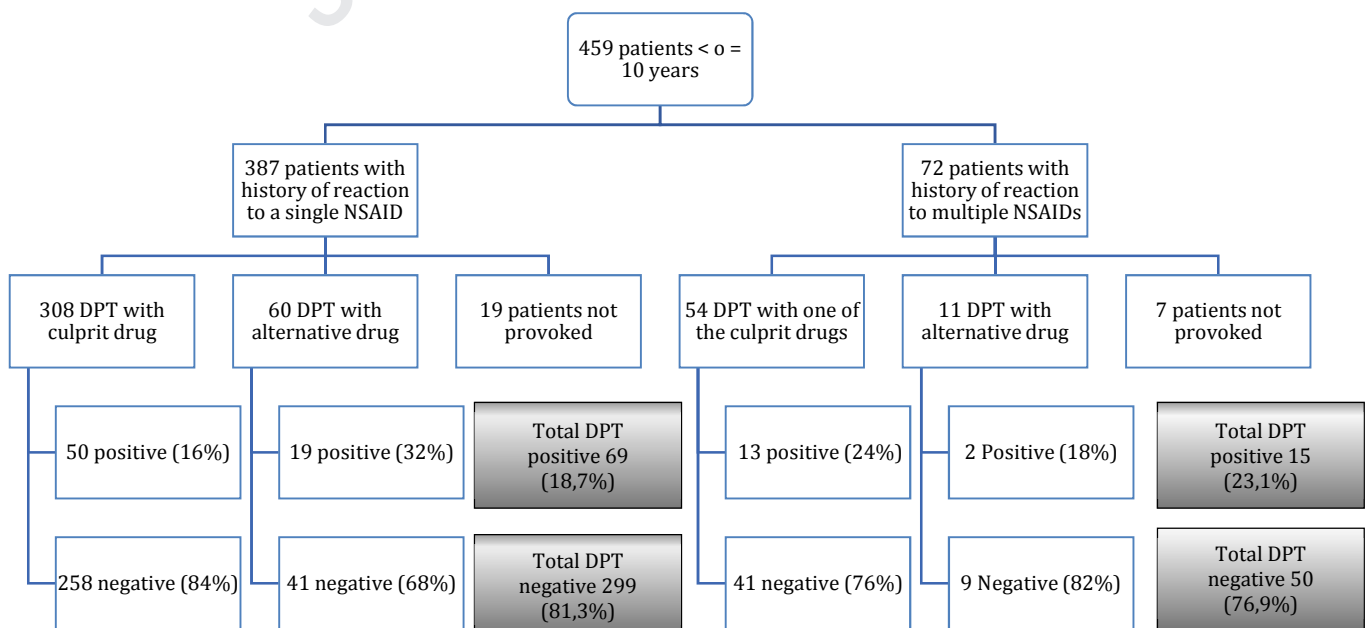
NoR: total number of reactions

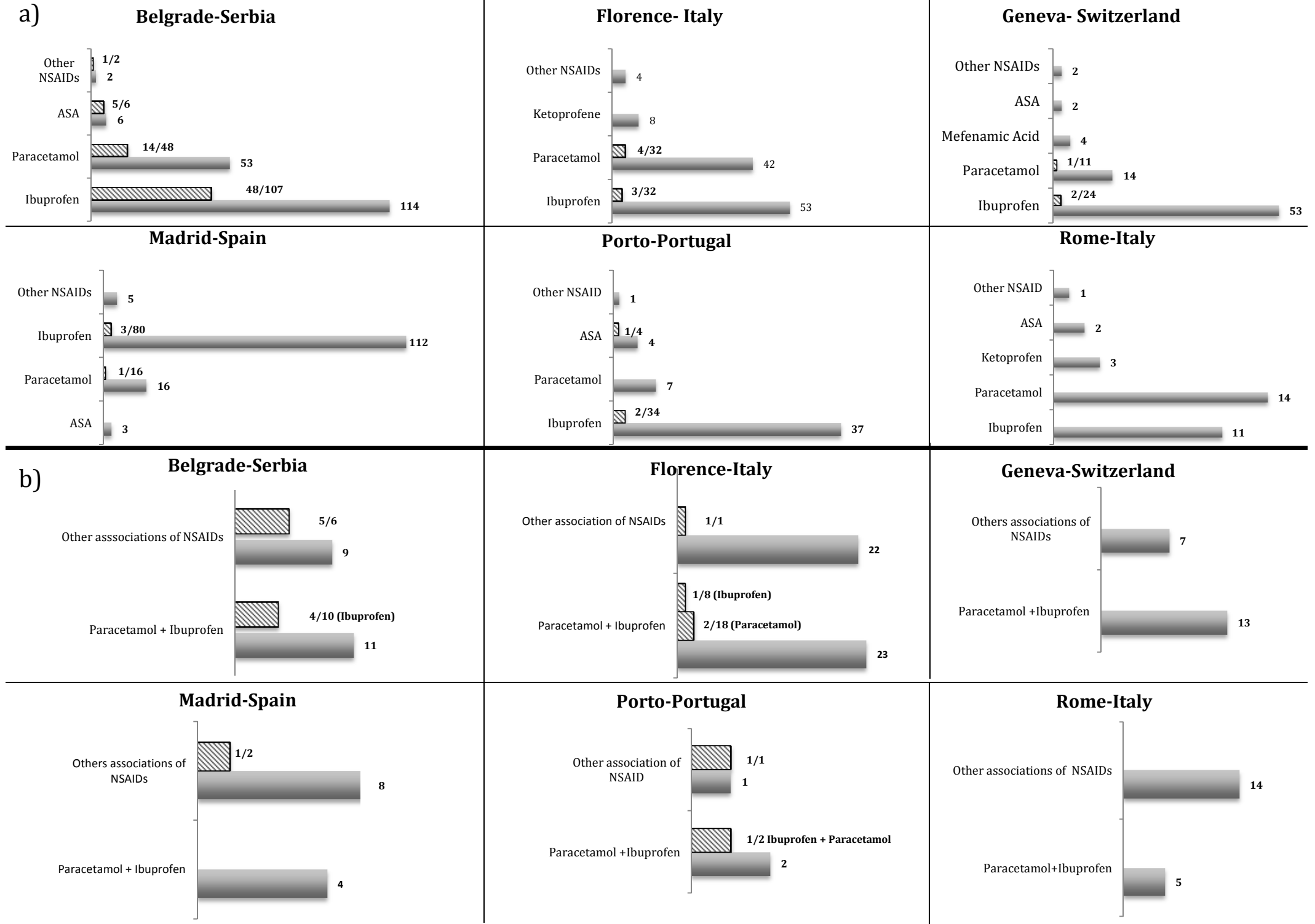
FIGURE II. Summation of all the DPT results

a)



b)





Belgrade-Serbia

Association	Clinical history (absolute number)	Positive DPT (fraction)
Other associations of NSAIDs	9	5/6
Paracetamol + Ibuprofen	11	4/10 (Ibuprofen)

Florence-Italy

Association	Clinical history (absolute number)	Positive DPT (fraction)
Other association of NSAIDs	22	1/1
Paracetamol + Ibuprofen	23	1/8 (Ibuprofen), 2/18 (Paracetamol)

Geneva-Switzerland

Association	Clinical history (absolute number)
Others associations of NSAIDs	7
Paracetamol +Ibuprofen	13

Madrid-Spain

Association	Clinical history (absolute number)	Positive DPT (fraction)
Others associations of NSAIDs	8	1/2
Paracetamol + Ibuprofen	4	-

Porto-Portugal

Association	Clinical history (absolute number)	Positive DPT (fraction)
Other association of NSAID	1	1/1
Paracetamol +Ibuprofen	2	1/2 Ibuprofen + Paracetamol

Rome-Italy

Association	Clinical history (absolute number)
Other associations of NSAIDs	14
Paracetamol+Ibuprofen	5

FIGURE I. a) ■ Clinical history of reaction to single NSAID (absolute number); ▨ positive DPT to culprit drug on total of DPTs performed. b) ■ Clinical history of reaction to multiple NSAIDs (absolute number); ▨ positive DPT to one of the culprit drug on total of children tested

c)

Implicated/culprit NSAID in patients with positive DPT

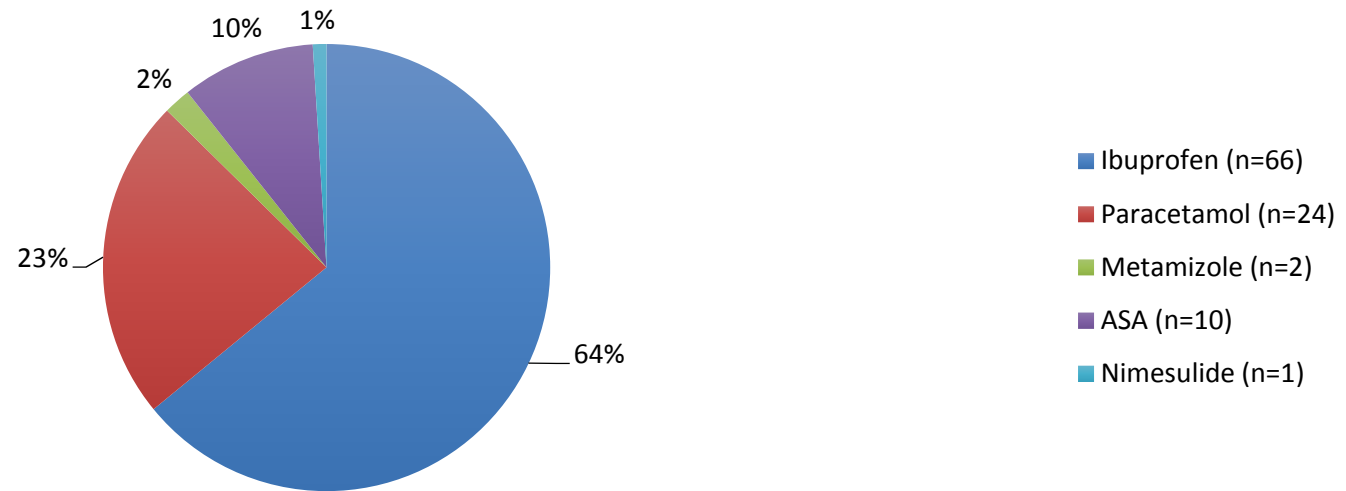


FIGURE I

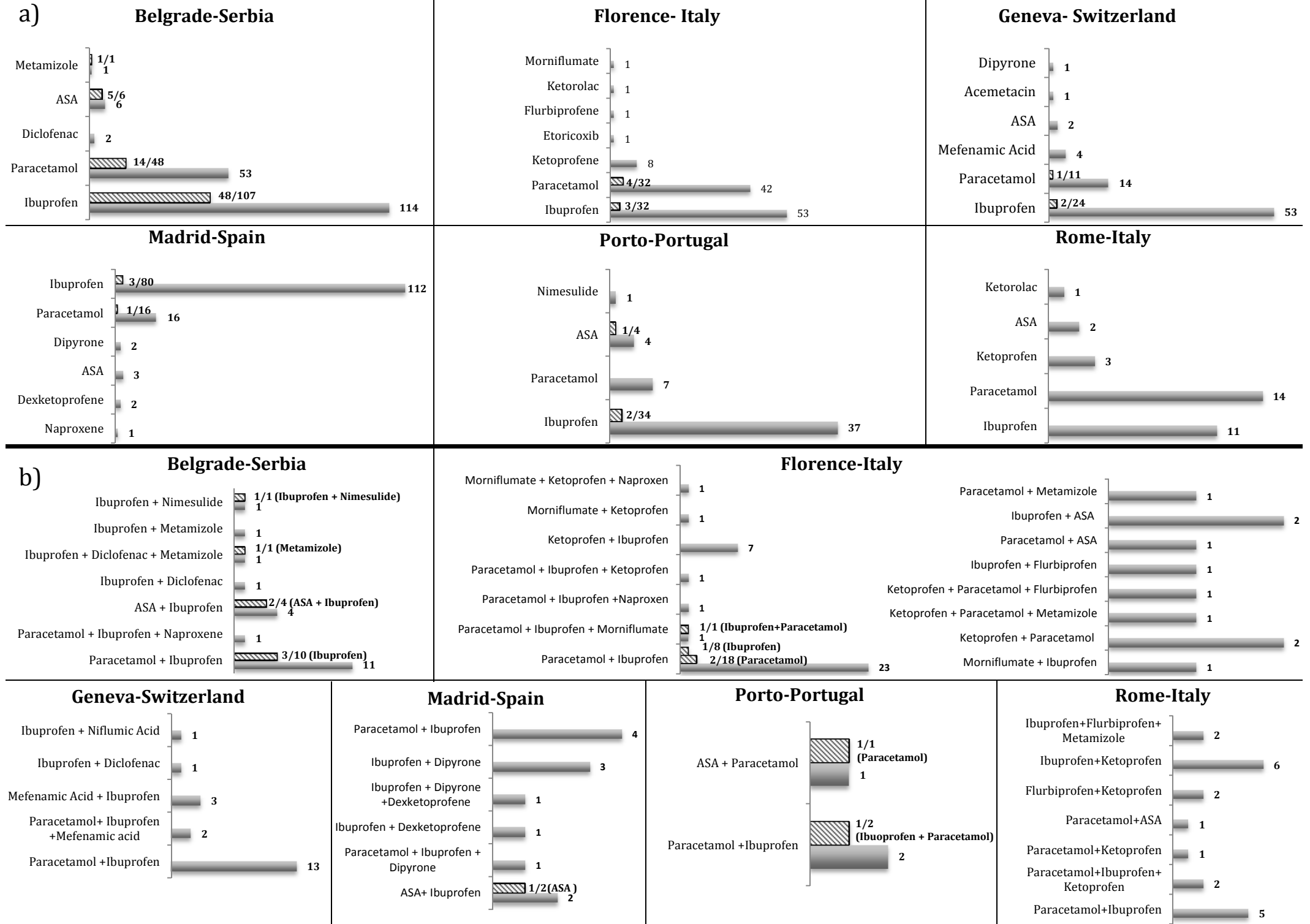


FIGURE I. a) ■ Clinical history of reaction to **single** NSAID (absolute number); ▨ positive DPT to culprit drug on total of DPTs performed. b) ■ Clinical history of reaction to **multiple** NSAIDs (absolute number); ▨ positive DPT to one of the culprit drug on total of children tested

FIGURE EI. a) Clinical history of reaction to single NSAID (absolute number); positive DPT to culprit drug on total of DPTs performed. b) Clinical history of reaction to multiple NSAIDs (absolute number); positive DPT to one of the culprit drug on total of children tested