

Metamizole intolerance and bronchial asthma

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SUMMARY

Background: Metamizole is one of the pyrazolone drugs used widely in Turkey. The aim of this survey was to determine the clinical features of metamizole intolerant patients and to find out if there was any difference between the ones with or without bronchial asthma.

Methods: A total of 264 patients with metamizole intolerance were enrolled in the survey. Patients having bronchial asthma were accepted as group I (n = 133) and the ones without bronchial asthma as group II (n = 131). A standard questionnaire was used to collect the data.

Results: The mean age of the patients were 41.8 ± 11.8 and 39.2 ± 12.2 for groups I and II respectively and 99 (79.4 %) and 99 (75.6 %) were females in the same order. There was no significant difference between groups I and II when the rates of personal atopy, familial atopy and familial analgesic intolerance were compared. The most common reactions appearing after metamizole ingestion was bronchospasm (75.9 and 9 %) and urticaria (25.6 and 64.9 %) (for groups I and II, respectively and $p < 0.05$). Aspirin cross-reactivity was significantly more common in group I. At least one safe alternative analgesic was determined for all the patients who have not been able to use any analgesic.

Conclusions: Metamizole intolerance seems to be as important as aspirin intolerance in Turkey. The clinical features in general appear to be similar for metamizole and aspirin intolerant asthmatics.

Key words: Analgesic intolerance. Aspirin intolerance. Bronchial asthma. Metamizole intolerance.

INTRODUCTION

The prevalence of analgesic intolerance in general population is about 1 % while it is about 10 % in adult asthmatics. The analgesic consumption accounted for 13.2 % and 12 % of the total drug consumption for the years of 1999 and 2000, respectively in Turkey (1). Since the prototype of this condition is aspirin intolerance and aspirin-induced asthma, there are many surveys and reports on these subjects in the literature. Metamizole is the second drug after aspirin causing intolerance in adults in Turkey according to previous reports of ours (2, 3). Although the use of metamizole is banned in some countries due to some of its side-effects like agranulocytosis it is still widely used in Turkey (4). The mean annual number of metamizole boxes reciped by the Turkish physicians for the last five years (1996-2000) as injectable and tablet forms is 14,376,100 (5). There are only case reports about metamizole intolerance (MI) in the literature (4-7) and some other papers mentioning metamizole (= dipyrone) intolerance among the NSAID intolerant patients (10, 11) and two papers about intolerance to pyrazolone drugs but not metamizole (12-14) and a letter comparing the provocation test results of sulfinpyrazone in patients with aspirin and metamizole intolerance, respectively (15).

The aim of this survey was to determine the clinical features of MI and to find out if there was any difference between MI patients with or without BA.

MATERIAL AND METHODS

Two hundred sixty four patients admitted to our adult allergy unit between January 1991 and July

2001 and diagnosed with metamizole intolerance were prospectively enrolled in the survey. Patients having BA were accepted as group I ($n = 133$) and the ones without BA as group II ($n = 131$).

A standard questionnaire was filled-in by two researchers who are both pulmonologist and allergologist for all the patients. Data was collected about the age, gender, age of diagnosis for BA, rhinosinusitis, MI and nasal polyps; features of MI (other analgesic(s) causing intolerance, latent period between the drug ingestion and the beginning of the reaction, the reactions emerged, duration of the reaction, cumulative analgesic consumption), other accompanying allergic diseases (antibiotic and food allergy/intolerance, metal allergy, dermatographism, chronic urticaria), the atopic status of the patient and his/her family, familial history of analgesic intolerance, smoking history and having pet animals at home. Number of boxes of analgesics that the patients had used until the appearance of MI was asked to the patients to assess the lifelong analgesic consumption (a regular analgesic box in Turkey contains 20 pills).

The diagnosis of asthma was made by history depending on the international guidelines (16). The diagnosis of MI and intolerance to other analgesics were made by history. Sufficient and reliable clinical history of at least two events with the same analgesic was required for MI and AI. The reaction should have occurred within three hours after the ingestion of the analgesic. If there was only one event, then confirmation by oral provocation test was required. Oral provocation with metamizole was performed only in 3 patients who only had one event after ingesting the drug and 2 of them reacted where the reactions were not life-threatening. One of them did not react to metamizole and has already been excluded from the study in the beginning. Oral provocation tests were performed as described before (1). Physical examination, chest radiography and pulmonary function testing were performed in all the patients.

Routine skin prick tests were performed to all the patients except for the ones who were pregnant, or had chronic urticaria and/or dermatographism or used antihistaminics at the time of the test ($n = 67$ for the total, $n = 28$ for group I and $n = 39$ for group II). Twelve standard antigen solutions (dermatophagoides pteronyssinus, phleum pratense, olea europa, artemisia vulgaris, parietaria officinalis, hazelnut, betula verrucosa, cat, dog, horse, alternaria alternata and cladosporium herbarum) were used which were prepared by ALK (Denmark) and Greer (USA) companies. The standard antigen solutions were applied before pricking the skin of the volar aspect of the forearm with a

special lancet having 1 mm tip. Histamine and saline were used as positive and negative controls, respectively. A wheal with perpendicular diameters of 3x3 mm or more was considered as positive reaction. Atopy was defined as a positive reaction to any one of the allergens. A positive familial history of atopy was considered when the patient reported a first-degree family member with the symptoms and/or diagnosis of asthma, allergic rhinitis and/or atopic dermatitis.

SPSS statistical package (SPSS for Windows, 9.0 release) was used for the analysis of the data. Metamizole intolerant patients with asthma were compared with the ones without asthma. The means and the standard deviations for the numerical variables were calculated. Comparison of the continuous variables between the two groups was performed by student t test or by Mann-Whitney U test for the ones with and without normal dispersion, respectively. Chi square (Yates' correction) test was used to compare the distribution of the categorical variables and was replaced by Fisher's exact test when the expected cell count was less than five. A p value of less than 0.05 was considered for statistical significance.

RESULTS

The demographic and the clinical features of the patients are shown in table I. The oral provocation test results which were performed to find out safe alternatives for the metamizole intolerant patients are shown in table II. At least one safe alternative analgesic was determined for all the patients who have not been able to use any analgesics.

DISCUSSION

Metamizole (= dipyrone) has been in clinical use since 1922 (3). Its use has been banned in some countries due to the risk of agranulocytosis. It is still one of the leading analgesic/antipyretic drugs in most of the Mediterranean countries including Turkey. Pyrazolone hypersensitivity can be of two distinct forms. One group of patients, usually with chronic asthma, have reactions similar to aspirin-induced asthma which probably involves prostaglandin inhibition and overproduction of cysteinyl leukotrienes. The other group of patients mainly develop anaphylaxis, urticaria and other forms of rash where the hypersensitivity presumably due to immunological mechanisms (12, 17). However, a mixed form is probably more common.

Table I
The demographic and clinical features and the SPT results of the patients

	MI Whole group (n = 264) n (%)	MI with BA Group I (n = 133) n (%)	MI without BA Group II (n = 131) n (%)
Mean age \pm SD	40.5 \pm 12.0	41.8 \pm 11.8	39.2 \pm 12.2
Gender (females)	198 (75)	99 (74.4)	99 (75.6)
At least one emergency room admission due to analgesic intolerance in the last year	163 (61.7)	73 (54.9)	90 (68.7)
Reactions emerging after metamizole ingestion			
Bronchospasm	114 (43.2)	101 (75.9)*	13 (9.9)
Urticaria	119 (45.1)	34 (25.6)	85 (64.9)*
Angioedema	114 (43.2)	29 (21.8)	85 (64.9)*
Exanthematous skin lesions	52 (19.7)	24 (18)	28 (21.4)
Anaphylaxis	35 (13.3)	16 (12)	19 (14.5)
Rhinitis	13 (4.9)	6 (4.5)	7 (5.3)
Gastrointestinal symptoms	5 (1.9)	3 (2.3)*	2 (1.5)
Fixed eruption	2 (0.8)	1 (0.8)	1 (0.8)
Mean time interval between the ingestion and the reaction \pm SD (minutes)	34.6 \pm 45.8	34.4 \pm 44.6	34.8 \pm 47.3
Mean duration of the reaction \pm SD (hours)	8.1 \pm 14.1	6.1 \pm 11.3*	10.1 \pm 16.3
Cumulative analgesic consumption (boxes)	10.5 \pm 12.5	12.1 \pm 15.5	8.6 \pm 6.9*
Intolerance to other analgesics			
Aspirin	156 (59.1)	89 (66.9)*	67 (51.1)
Paracetamole	58 (22)	24 (18)	34 (26)
Naproxen	46 (17.4)	24 (18)	22 (16.8)
Others	30 (11.4)	14 (10.5)	16 (12.2)
Isolated metamizole intolerance	19 (7.2)	18 (9.8)	6 (4.6)
Nimesulide	5 (0.4)	2 (1.5)	3 (2.3)
Most common reason for taking an analgesic			
Headache	178 (67.4)	98 (73.7)*	80 (61.1)
Dysmenore	55 (20.8)	18 (13.5)	37 (28.2)*
Arthralgia	25 (9.5)	12 (9)	13 (9.9)
Tooth ache	22 (8.3)	4 (3.0)	18 (13.7)*
Other	20 (7.6)	11 (8.3)	9 (6.9)
Accompanying allergic conditions			
Food allergy/intolerance	60 (22.7)	33 (24.8)	27 (20.6)
Antibiotic allergy/intolerance	50 (18.9)	24 (18)	26 (19.8)
Metal allergy	43 (16.3)	20 (15)	23 (17.6)
Chronic urticaria	41 (15.5)	19 (14.3)	22 (16.8)
Dermographism	35 (13.3)	15 (11.3)	20 (15.3)
Familial atopy	133 (50.4)	71 (53.4)	62 (47.3)
Familial analgesic intolerance	29 (11)	10 (7.5)	19 (14.5) (p = 0.052)
Current smoking	73 (27.2)	35 (26.3)	38 (29)
Pet animals	39 (14.8)	18 (13.5)	21 (16)
Skin prick test			
Positive	56 (28.4)	33 (31.4)	23 (25)
Negative	141 (71.6)	72 (68.6)	69 (75)

* = p < 0.05

Table II
The oral provocation test results which were performed to find out safe alternatives

	MI whole group		MI with BA group I		MI without BA group II	
	Tests N = 166 n (%)	Positive tests n (%)	Tests N = 73 n (%)	Positive tests n (%)	Tests N = 93 n n (%)	Positive tests n (%)
Codeine	94 (56.6)	10 (10.6)	46 (63)	6 (13.0)	48 (51.6)	4 (8.3)
Paracetamole	82 (49.4)	12 (14.6)	33 (45.2)	7 (21.2)	49 (52.7)	5 (10.2)
Nimesulide	66 (39.8)	9 (13.6)	25 (34.2)	7 (28)	41 (44.1)	2 (4.9)
Meloxicam	54 (32.5)	6 (11.1)	23 (31.5)	4 (17.4)	31 (33.3)	2 (6.5)
Rofexocib	28 (16.9)	2 (7.1)	14 (19.2)	2 (14.3)	14 (15.1)	0
Sodium salicylate	15 (9.0)	4 (26.7)	6 (8.2)	4 (66.7)	9 (9.7)	0

To our knowledge, this is the largest series about metamizole intolerance in the literature. The mean age of the patients are in the fourth decade and they are mostly (75 %) females. There is a large series of 68 pyrazolone intolerant patients in the literature and metamizole intolerance is not included in the paper (12). The mean age of the patients were in the fourth decade and they were also mostly females (12). In two other series of 46 and 91 patients pyrazolone intolerance and noramidopyrine, propiphenazone and feprazone intolerance were studied (13, 14). There is also a letter in which the results of the provocation tests with sulfinpyrazone were reported in two groups of patients one having AIA ($n = 11$) and the other dipyrone intolerance ($n = 11$) (15). Since the aims and the study groups were not comparable, comparison of the results of these studies and ours has some limitations.

When our patients are taken as a whole group the three most common reactions are bronchospasm, urticaria and angioedema (43.2 %, 45.1 % and 43.2 %, respectively). When the groups are divided into two according to having asthma or not bronchospasm is significantly more common in group I (75.9 % versus 9.9 %, $p < 0.05$) whereas urticaria and angioedema are significantly more common in group II (25.6 % versus 64.9 % for urticaria; and 21.8 % versus 64.9 % for angioedema, $p < 0.05$). This is in accordance with the literature where generally analgesic intolerance is taken into consideration (1, 2, 10, 34). There is no significant difference between the groups when the mean time interval between the drug ingestion and the appearance of the reactions are compared, but the mean duration of the reactions is significantly shorter in the MI with BA group compared to the ones without BA (6.1 ± 11.3 versus 10.1 ± 16.3 hours, respectively and $p < 0.05$). This might be due to the domination of

bronchospastic reactions in the group with BA and bronchospastic reactions might recover in a shorter time compared to the urticarial lesions. The amount of analgesic consumption is significantly higher in group I compared to group II (12.1 ± 15.5 versus 8.6 ± 6.9 for group I and II, respectively and $p < 0.05$). This is in accordance with our previous reports where we also found significantly higher analgesic consumption rates in patients with analgesic-induced asthma compared to the group having only asthma (2). In the other survey of ours, AIA patients had a higher rate of analgesic consumption than AI patients without asthma, although this difference did not reach statistical significance (3). Although showing conflicting results, there are some reports which suggested some associations between the use of paracetamole and other analgesics and severity of asthma in the literature (18, 19).

Aspirin is the drug showing the most common cross-intolerance to metamizole in the whole group and groups I and II; and aspirin intolerance is significantly more common in group I compared to group II (66.9 % versus 51.1 %, respectively and $p < 0.05$). This might be an indicator of strong relation between asthma and aspirin intolerance apart from MI. Accompanying allergic conditions are similar to the ones previously reported in analgesic intolerant patients (1, 2).

The rate of atopy according to skin prick test positivity shows no significant difference when the two groups having BA and not having BA are compared. There are conflicting reports about atopy in analgesic intolerant patients in the literature. In some papers the rate of atopy ranges between 3 % and 65 % (2, 3, 20-23) and in others there is no atopy (17, 24, 25). These variations might be due to the methodological differences as we mentioned before (2, 3). The rate of familial atopy is similar within the

groups (53.4 % versus 47.3 %) which is in accordance with previous reports in aspirin intolerants (2, 3, 40, 41), but the rate of familial analgesic intolerance is, although statistically not significant, less common in the group having BA (7.5 % versus 14.5 %, $p = 0.052$). In one of our previous surveys (2) it was less common in the group with BA although not significant statistically. In another survey of ours analgesic intolerant group with BA had a familial history of analgesic intolerance at a rate of 4.5 % and in the group having only analgesic intolerance none had it. Although these results are not statistically significant, they might seem conflicting which may be due to recall bias and/or to the increasing experience and awareness of the researchers on the subject.

None of the patients in group II showed a reaction to sodium salicylate in the oral provocation tests (reaction rate 66.7 % for group I and 0 for group II, respectively and $p = 0.01$), which is an interesting result quite hard to interpret.

In conclusion, metamizole is still used widely in some countries as a cheap analgesic-antipyretic drug and MI is as important as aspirin intolerance in these countries. When the general features are taken into consideration metamizole intolerant patients are not much different from the aspirin intolerant and/or aspirin-induced asthmatic ones. Consequently, all these patients might be placed under the title of analgesic intolerance or analgesic-induced asthma (26). An alternative analgesic can always be found by oral provocation tests in MI. Since aspirin intolerance is more common and the rate of cumulative life long consumption of analgesics is higher in the asthmatic group, there seems to be a direct relation between analgesic (especially aspirin) consumption and asthma. There is not any standard laboratory marker for analgesic intolerance including MI for the time being, but the searches are going on. The most reliable marker for MI is clinical which is a history of reaction at least on two occasions or oral provocation test with metamizole if there is only one episode of reactions.

RESUMEN

Información básica: El metamizol es una de las pizolonas empleadas de forma generalizada en Turquía. El objetivo de este estudio era determinar las características clínicas de los pacientes intolerantes al metamizol e investigar si había diferencias en los pacientes con asma bronquial y aquellos sin asma.

Métodos: Se inscribió en el estudio a un total de 264 pacientes con intolerancia al metamizol. Los pacientes con asma bronquial formaron el grupo I ($n = 133$) y los enfermos sin asma, el grupo II ($n = 131$). Se utilizó un cuestionario normalizado para recoger los datos.

Resultados: El promedio de edad de los pacientes era de $41,8 \pm 11,8$ y $39,2 \pm 12,2$ años en los grupos I y II, respectivamente, y había 99 mujeres en el grupo I (79,4 %) y 99 en el grupo II (75,6 %). No se observaron diferencias significativas entre los grupos I y II al comparar las tasas de atopia personal, atopia familiar e intolerancia familiar a los analgésicos. Las reacciones más frecuentes que surgieron tras la ingestión de metamizol fueron broncospasmo (75,9 y 9 %) y urticaria (25,6 y 64,9 %) (en los grupos I y II, respectivamente, y $p < 0,05$). La reactividad cruzada con el ácido acetilsalicílico fue significativamente más frecuente en el grupo I. Se identificó al menos un analgésico alternativo inocuo en todos los pacientes que no habían sido capaces de tomar ningún analgésico.

Conclusiones: La intolerancia al metamizol parece ser tan importante como la intolerancia al ácido acetilsalicílico en Turquía. En general, las características clínicas de los asmáticos con intolerancia al metamizol o al ácido acetilsalicílico parecen ser semejantes.

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Palabras clave: Intolerancia a los analgésicos. Intolerancia al ácido acetilsalicílico. Asma bronquial. Intolerancia al metamizol.

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