World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v22.i5.1877

World J Gastroenterol 2016 February 7; 22(5): 1877-1883
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Observational Study

Italian survey on non-steroidal anti-inflammatory drugs and gastrointestinal bleeding in children

Sabrina Cardile, Massimo Martinelli, Arrigo Barabino, Paolo Gandullia, Salvatore Oliva, Giovanni Di Nardo, Luigi Dall'Oglio, Francesca Rea, Gian Luigi de' Angelis, Barbara Bizzarri, Graziella Guariso, Enzo Masci, Annamaria Staiano, Erasmo Miele, Claudio Romano

Sabrina Cardile, Claudio Romano, Gastroenterology and Endoscopic Unit, Department of Pediatrics, University of Messina, 98100 Messina, Italy

Massimo Martinelli, Annamaria Staiano, Erasmo Miele, Department of Translational Medical Science, Section of Pediatrics, University of Naples "Federico II", 80131 Naples, Italy

Arrigo Barabino, Paolo Gandullia, Department of Pediatric Gastroenterology, Gaslini Institute, 16148 Genoa, Italy

Salvatore Oliva, Giovanni Di Nardo, Department of Pediatrics and Infantile Neuropsychiatry, Pediatric Gastroenterology and Liver Unit, Sapienza University of Rome, 00185 Rome, Italy

Luigi Dall'Oglio, Francesca Rea, Digestive Surgery and Endoscopy Unit, Bambino Gesù Children's Hospital, 00165 Rome, Italy

Gian Luigi de' Angelis, Barbara Bizzarri, Gastroenterology and Endoscopy Service, University of Parma, 43126 Parma, Italy

Graziella Guariso, Unit of Paediatric Gastroenterology, Digestive Endoscopy, Hepatology, and Care of Children with Liver Transplantation, Department of Women's and Children's Health, University Hospital of Padova, 35128 Padova, Italy

Enzo Masci, Gastrointestinal Endoscopy, Azienda Ospedaliera San Paolo University Hospital, University of Milan, 20142 Milan, Italy

Author contributions: Cardile S and Martinelli M contributed equally to this study, who performed review of the literature and drafted the manuscript; the other authors provided the data of patients, and participated in the design of the study and in the revision of manuscript; Romano C conceived and coordinated the study; all authors have read and approved the final manuscript to be published.

Institutional review board statement: The study was reviewed and approved by the Scientific Committee of the coordinating Unit (University of Messina). Prot. E 37/12, 07/09/2012.

Informed consent statement: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained in verbal form from all individual participants included in the study.

Conflict-of-interest statement: All authors declare that they have no conflict of interest. The data presented, the statements made, and the views expressed are solely the responsibility of the authors.

Data sharing statement: Consent was not obtained but the presented data are anonymized and risk of identification is low.

Correspondence to: Claudio Romano, MD, Gastroenterology and Endoscopic Unit, Department of Pediatrics, University of Messina, Via Consolare Valeria, 98100 Messina, Italy. romanoc@unime.it
Telephone: +39-90-22129189
Fax: +39-90-2213877

Received: August 28, 2015
Peer-review started: September 5, 2015
First decision: September 29, 2015
Revised: October 13, 2015
Accepted: November 13, 2015
Article in press: November 13, 2015
Published online: February 7, 2016

Abstract

AIM: To investigate gastrointestinal complications associated with non-steroidal anti-inflammatory drug (NSAIDs) use in children.

METHODS: A retrospective, multicenter study was conducted between January 2005 and January 2013, with the participation of 8 Italian pediatric gastroenterology centers. We collected all the cases of patients who refer to emergency room for suspected gastrointestinal bleeding following NSAIDs consumption, and underwent endoscopic evaluation. Previous medical history, associated risk factors, symptoms and signs at presentation, diagnostic procedures, severity of bleeding and management of gastrointestinal bleeding were collected. In addition, data regarding type of drug used, indication, dose, duration of treatment and prescriber (physician or self-medication) were examined.

RESULTS: Fifty-one patients, including 34 males, were enrolled (median age: 7.8 years). Ibuprofen was the most used NSAID [35/51 patients (68.6%)]. Pain was the most frequent indication for NSAIDs use [29/51 patients (56.9%)]. Seven patients had positive family history of *Helicobacter pylori* (*H. pylori*) infection or peptic ulcer, and 12 had associated comorbidities. Twenty-four (47%) out of 51 patients used medication inappropriately. Hematemesis was the most frequent symptom (33.3%). Upper gastrointestinal endoscopy revealed gastric lesions in 32/51 (62%) patients, duodenal lesions in 17 (33%) and esophageal lesions in 8 (15%). In 10/51 (19.6%) patients, a diagnosis of *H. pylori* gastritis was made. Forty-eight (94%) patients underwent medical therapy, with spontaneous bleeding resolution, while in 3/51 (6%) patients, an endoscopic hemostasis was needed.

CONCLUSION: The data collected in this study confirms that adverse events with the involvement of the gastrointestinal tract secondary to NSAID use are also common in children

Key words: Hematemesis; Gastrointestinal bleeding; Non-steroidal anti-inflammatory drug; Melena; Pediatrics

Core tip: It is known that non-steroidal anti-inflammatory drug (NSAIDs) are one of the most extensively used medications. Adverse effects associated with their use are commonly reported in the gastrointestinal tract. Data on children are limited and evidence is based mainly on case reports, and relatively small cohort studies. Our manuscript represents the first Italian survey focusing on gastrointestinal bleeding occurrences following NSAIDs consumption in a pediatric population. A high number of self-prescriptions and inappropriate use represent the most alarming data. Our data show that the risk of adverse events seems to be related to improper use rather than to NSAIDs safety profile.

Cardile S, Martinelli M, Barabino A, Gandullia P, Oliva S, Di Nardo G, Dall'Oglio L, Rea F, de' Angelis GL, Bizzarri B, Guariso G, Masci E, Staiano A, Miele E, Romano C. Italian survey on non-steroidal anti-inflammatory drugs and gastrointestinal bleeding in children. *World J Gastroenterol* 2016; 22(5): 1877-1883 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i5/1877.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i5.1877

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are perhaps some of the most extensively used medications in the world for their anti-inflammatory and antipyretic effects, in both adults and children[1,2]. They are frequently used for fever control and are generally considered to be safe. Despite their benefits, there is evidence for gastrointestinal (GI) complications, including peptic ulcer disease, bleeding and perforation. These GI events result in more than 100000 hospitalizations annually in the United States and in 7000-10000 deaths, especially among those who belong to high-risk categories[3-5]. The pathogenesis of NSAID gastrointestinal toxicity is topical injury to the mucosa, and systemic effects associated with mucosal prostaglandin depletion derived from COX-1[6]. Adverse effects associated with the use of NSAIDs are most commonly reported in the upper GI tract; and in addition to damage to the gastric mucosa, NSAIDs may also cause mucosal damage in the small intestine and colon[7]. The clinical presentation of GI complications from NSAIDs is not always typical, since many patients may have non-specific symptoms and signs, such as dyspepsia, nausea, vomiting, abdominal pain, diarrhea and anemia. Only acute GI bleeding (hematemesis and/or melena) is considered the typical clinical manifestation of peptic damage from NSAIDs[5]. Data on children are, however, limited, and the evidence is based mainly on case reports, series and relatively small cohorts[8-13]. NSAIDs were associated with 12 out of 390 fatal events (0.03%) in a British study conducted from 1990 to 2000[11]. In another survey, among children affected by rheumatoid arthritis on long-term treatment with NSAIDs, more than 75% of patients had abdominal pain, gastritis, antral erosions or ulcers[12]. More recently, Grimaldi-Bensouda *et al*[13] reported that 83 out of 177 (46.9%) children with upper gastrointestinal bleeding (UGIB) had taken NSAIDs at least once before the index date, with an adjusted odds ratio (OR) of 8.2. GI complications related to the use of NSAIDs is therefore well known and well studied in the

Table 1 Baseline characteristics of 51 patients with gastrointestinal bleeding following non-steroidal anti-inflammatory drug consumption *n* (%)

Characteristics	Patients
Median age (range)	7.6 yr (5 mo-15.3 yr)
Gender	
Male	34 (66.7)
Female	17 (33.3)
Indications for drug use	
Pain	29 (56.9)
Fever	21 (41.2)
Inflammation	1 (2)
Comorbidities (n = 12)	
Cardiovascular disease	1 (2)
Celiac disease	1 (2)
Cystic fibrosis	1 (2)
Diaphragmatic hernia	1 (2)
GERD	1 (2)
H. pylori infection	3 (5.9)
IBD	1 (2)
Neurological diseases/cognitive impairment	2 (3.9)
Pulmonary atelectasis	1 (2)
Other medications (n = 19)	
Corticosteroids	7 (13.7)
Antibiotics	10 (19.6)
Acetaminophen	1 (2)
Baclofen	1 (2)

H. pylori: *Helicobacter pylori*; GERD: Gastroesophageal reflux disease; IBD: Inflammatory bowel disease; NSAIDs: Non-steroidal anti-inflammatory drugs.

adult population, but studies are needed in pediatrics in order to define preventive strategies. The primary aim of our survey was to retrospectively collect all the cases of GI bleeding following NSAIDs consumption in the Italian pediatric population; as a secondary aim, we also evaluated appropriateness of the prescription, clinical presentation, and correlated risk factors.

MATERIALS AND METHODS

A retrospective, multicenter study was conducted, with the participation of eight Italian pediatric gastroenterology centers. All the centers involved were asked to retrospectively collect data from pediatric patients who had presented at the emergency room for suspected gastrointestinal bleeding, following NSAIDs consumption. The cases were collected from January 2005 to January 2013. Previous medical history, symptoms and signs at presentation, diagnostic procedures, severity of bleeding and treatment to manage GI bleeding were collected. Endoscopic procedure was considered an emergency treatment if carried out within 12 h from GI bleeding, while all the procedures performed after 12 h were considered elective treatments. Physicians were required to report endoscopy findings, if performed. Esophageal damage was described according to the Los Angeles Classification[14]. Forrest classification was used to describe ulcerations[15]. Risk factors, including portal hypertension, history of GI bleeding or peptic disease, gastro-oesophageal reflux disease (GERD), *Helicobacter pylori* (*H. pylori*) infection and coagulation disorders were also recorded. In addition, data regarding type of drug used, indication, dose, duration of treatment and prescriber (physician or self-medication) were collected. The appropriateness of drug use was also evaluated. It was considered inappropriate if the weight-dose, number of administrations per day or age of the patient were not in accordance with the Package Inserts of the drug. Informed consent was obtained from the parents of participating children. The study was approved by the Scientific Committee of the Coordinating Unit (University of Messina, Prot. E 37/12, 07/09/2012).

Statistical analysis

Variables were screened for distribution, and appropriate parametric or non-parametric tests were adopted as necessary. The Student's t test, the Mann-Whitney test for continuous variables, and the χ^2 and Fisher's exact tests for categorical variables were used where appropriate. In order to distinguish age-based differences, enrolled children were divided into three subgroups: age $\leqslant$ 3 years; age > 3 years $\leqslant$ 7 years; age > 7 years. Statistical significance was predetermined as $P < 0.05$. Percentages were rounded to the nearest whole numbers. SPSS version 20 was used for all statistical analyses.

RESULTS

Fifty-one patients, including 34 males, were enrolled in the study (median age: 7.8 years; range 5 mo to 18 years) between January 2005 and January 2013. Baseline characteristics of the enrolled patients are shown in Table 1. There was a progressive increase of cases between 2005 and 2013, with the highest number of cases reported in 2011 [18/51 (35.2%)].

Drug use and indications

Ibuprofen was the most used NSAID [35/51 (68.6%)], followed by ketoprofen [5/51 (9.8%)] and acetylsalicylic acid [4/51(7.8%)]. Other NSAIDs used included flurbiprofen, ketoralac, naproxen, niflumic acid and nimesulide. All NSAIDs associated with GI bleeding are shown in Table 2. Patients' age was significantly lower in those using ibuprofen compared with patients taking other NSAIDs [median age 5.5 years, range 5 mo-15 years *vs* median age 11 years, range 2.2-15 years; P = 0.004)]. Pain was the most frequent indication for NSAIDs use, being reported in 29 of 51 patients (56.9%), followed by fever [21/51 patients (41%)], and inflammation [(1/51 (2%)] (Table 1). The median duration of NSAID use prior to bleeding was 4 d (range 1-263 d). An analysis of the appropriateness of drug use showed that 24 (47%) of 51 patients used medications inappropriately in terms of weight-appropriate dose [8/24 (33.3%)], number of

Table 2 Reports on non-steroidal anti-inflammatory drugs *n* (%)

NSAIDs	Patients	Age (mo)	Male gender	Dose (mg/kg)	No. of administrations	Duration (d)
Ibuprofen	35 (68.6)	66 (5-183)	20 (57.1)	10 (8-50)	7 (1-18)	4 (1-263)
Ketoprofen	5 (9.8)	125 (27-180)	4 (80)	2 (1-3)	4 (2-15)	5 (1-18)
Acetylsalicic ac.	4 (7.8)	143.5 (113-170)	3 (75)	60 (5-200)	2.5 (1-22)	14 (2-25)
Flurbiprofen	3 (5.9)	100 (73-116)	3 (100)	20 (3-25)	6 (4-9)	4 (3-4)
Ketoralac	1 (2)	142	1 (100)	3	1	1
Naproxen	1 (2)	76	1 (100)	25	5	2
Niflumic ac.	1 (2)	139	1 (100)	25	10	5
Nimesulide	1 (2)	166	1 (100)	2	2	6

Continuous variables are expressed as median and range. ac: Acid; NSAIDs: Non-steroidal anti-inflammatory drugs.

Table 3 Appropriateness of use and medical prescription of non-steroidal anti-inflammatory drugs *n* (%)

NSAIDs (*n*)	Inappropriate use[1]			Medical prescription
	Weight-dose	No. of administrations/d	Age	
Ibuprofen (35)	4 (11.4)	10 (28.5)	0	26 (74.3)
Ketoprofen (5)	1 (20)	2 (40)	0	3 (60)
Acetylsalicic ac. (4)	0	0	4 (100)	1 (25)
Flurbiprofen (3)	2 (66.7)	2 (66.7)	0	2 (66.7)
Ketoralac (1)	0	1 (100)	0	1 (100)
Naproxen (1)	1 (100)	0	0	1 (100)
Niflumic ac. (1)	0	0	0	1 (100)
Nimesulide (1)	0	0	0	0

[1]Number of patients inappropriately using NSAIDs in terms of weight-dose, number of administrations per day, and age. ac: Acid; NSAIDs: Non-steroidal anti-inflammatory drugs.

administrations per day [15/24 (62.5%)] and age of patients [4/24 (16.6%)]. In 31 (31.4%) of 51 patients, NSAIDs were taken without a medical prescription (Table 3).

Clinical features

Hematemesis was the most frequent symptom, being present in 17 of 51 patients (33.3%). Age of children presenting with hematemesis was lower when compared to those with other symptoms, with a trend towards statistical significance [median age 6.1 years, range 5 mo-15 years *vs* median age 8 years, range 1.4-15.2 years; $P = 0.08$)]. Sixteen out of 51 patients (31.3%) reported abdominal pain and heartburn, while melena was the main symptom in 4 of 51 patients (7.8%). Anemia was the only sign in 13 patients (25%). One patient experienced nausea and vomiting (1.9%).

Endoscopic findings

All patients included in this study underwent upper GI endoscopy to exclude the presence of mucosal lesions. In 2 of 51 (3.9%) patients, ileocolonoscopy was also performed. Thirty-one of 51 patients (61%) required an emergency procedure, while in 20 patients (39%), the procedure was performed electively. Upper GI endoscopy confirmed the presence of gastric lesions in 32 (62%) of 51 patients, duodenal lesions in 17 (33%) and esophageal lesions in 8 (15%). Upper GI endoscopic lesions varied in different age groups. Younger children (age $\leqslant$ 3 years) showed more proximal lesions (esophageal and gastric) compared with older age groups (100% *vs* 82.7% *vs* 62.5%, $P = 0.04$). Duodenal lesions were significantly more in the oldest group (> 7 years) (37.5% *vs* 18.5% *vs* 0%, $P = 0.04$). Colonic lesions were documented in 2 of 51 patients. Detailed endoscopic findings are shown in Table 4.

Additional risk factors for GI bleeding

Twelve (23.5%) of 51 patients had associated comorbidities (Table 1). A family history of peptic disease was identified in 5/51 (9.8%) patients. In 3 (5.8%) of 51 patients, a family history of *H. pylori* was recorded, while in 10 (19.6%) of 51 patients, a histologic diagnosis of *H. pylori* active gastritis was made. Nineteen (37.3%) patients had taken other drugs contemporarily, including steroids [7/19 (36.8%)], antibiotics [10/19 (52.6%)], acetaminophen [1/19 (5.3%)], and baclofen [1/19 (5.3%)]. Five (9.8%) patients were taking gastro-protective drugs, including proton pump inhibitors (PPI) (4 patients) and H2 receptor antagonists (H2RAs) (1 patient). The duration of therapy [median 6 d (range 5-19 d) *vs* median 3.5 d (range 1-263 d), $P = 0.02$] and number of administrations [median 12 (range 8-18) *vs* median 6 (range 1-22), $P = 0.03$] were significantly higher in those patients using gastro-protective drugs

Therapeutic management

Forty-eight (94%) of 51 patients underwent medical therapy [PPIs: 47 patients (98%); H2RAs: 1 patient (2%)] with spontaneous bleeding resolution. In 3 patients (6%), an endoscopic hemostasis was needed (2 thermic and 1 mechanical). One (50%) of these 3 patients experienced re-bleeding after 48 hours with the need of a second endoscopic examination. No case required surgical treatment.

DISCUSSION

To the best of our knowledge, this is the first Italian survey focusing on GI bleeding occurrences following NSAIDs consumption in a pediatric population.

Table 4 Detailed endoscopic findings in 51 patients presenting with gastrointestinal bleeding after non-steroidal anti-inflammatory drug use *n* (%)

Variables	⩽ 3 yr (*n* = 11)	> 3 ⩽ 7 yr (*n* = 14)	> 7 ⩽ 16 yr (*n* = 26)	*P* value
Upper GI lesions				0.04
Proximal (esophagus and stomach)	10 (100)	12 (85.7)	15 (62.5)	
Distal (duodenum)	0	2 (14.3)	9 (37.5)	
Location				0.06
Esophagus	2 (18.1)	2 (14.3)	4 (15.4)	
Stomach	8 (72.7)	10 (71.4)	11 (42.3)	
Duodenum	0	2 (14.3)	9 (34.6)	
Colon	1 (9)	0	1 (3.8)	
Esophagus				0.90
Upper	0	0	0	
Middle	0	0	0	
Lower	2 (18.1)	2 (14.3)	4 (15.3)	
Los Angeles classification				0.50
Grade A	2 (100)	2 (100)	3 (75)	
Grade B	0	0	1 (25)	
Grade C	0	0	0	
Grade D	0	0	0	
Stomach				0.09
Antrum	0	0	4 (36.4)	
Body	4 (50)	4 (40)	3 (27.3)	
Fundus	4 (50)	6 (60)	4 (36.4)	
Type of lesions				0.40
Erythema	5 (62.5)	8 (80)	4 (36.4)	
Edema	0	1 (10)	1 (9.1)	
Erosions	2 (25)	1 (10)	3 (27.3)	
Ulcerations	1 (12.5)	0	3 (27.3)	
Duodenum				1.00
Bulb	0	2 (100)	8 (88.9)	
Duodenum	0	0	1 (11.1)	
Type of lesions				0.02
Nodularity	0	1 (50)	1 (11.1)	
Erythema	0	1 (50)	0	
Erosions	0	0	0	
Ulcerations	0	0	8 (88.8)	
Forrest Classification for ulcerations				0.30
Grade 1a	0	0	2 (18.2)	
Grade 1b	0	0	1 (9.1)	
Grade 2a	1 (100)	0	2 (18.2)	
Grade 2b	0	0	0	
Grade 2c	0	0	2 (15.4)	
Grade 3	0	0	6 (54.5)	
Colon				
Transverse	1 (9)	0	0	
Sigmoid	0	0	1 (3.8)	
Type of lesions				
Erythema	1 (100)	0	0	
Edema	0	0	1 (100)	

GI: Gastrointestinal; NSAIDs: Non-steroidal anti-inflammatory drugs.

Recently, Bianciotto *et al*[16], on behalf of the Italian Multicenter Study Group for Drug and Vaccine Safety in Children, reported an increased risk of UGIB associated with use of drugs, including NSAIDs, oral steroids and antibiotics. These data are in agreement with a warning published in 2010 by the Italian Drug Agency (AIFA), which warned of a significant increase of adverse NSAID-related reactions in children[17]. This increase was mainly referred to the rise of ibuprofen prescriptions from 0.7 × 100.000 in 2005 to 1.7 × 100.000 in 2010[17]. Our data confirm a progressive increase of reports during the study-period. NSAIDs are commonly used agents in pediatrics for their anti-inflammatory, anti-pyretic and analgesic effects. Above all, ibuprofen use has been accepted, due to its safety profile, and demonstrated by two different large-scale studies[18,19]. These papers by Lesko *et al*[18,19], comparing the safety of acetaminophen and ibuprofen in children, showed no statistical differences in gastrointestinal complications, even if hospitalizations for GI bleeding occurred only in those patients receiving ibuprofen. Indeed, Bianciotto *et al*[16] reported an adjusted OR of 3.8 for ibuprofen-related GI bleeding, while Grimaldi-Bensouda *et al*[13] reported an OR of 10. Not surprisingly, ibuprofen was the most used drug among our patients, being associated with GI bleeding in 68.6% of cases. In addition, ibuprofen use was significantly frequent in younger patients, confirming the safety perception of prescribing doctors and families[16]. On the contrary, the number of reports concerning the use of acetylsalicylic acid, aspirin, is rather alarming. In all of these cases, aspirin use should be considered inappropriate, since aspirin is indicated exclusively in patients older than 16 years. These data are similar to those reported by Grimaldi-Bensouda *et al*[13] with striking difference that aspirin is not contraindicated in children in France. Nevertheless, the most alarming findings are those concerning NSAIDs prescription. Analysis of the appropriateness of drug consumption revealed that 47% of enrolled patients experienced an inappropriate use of medications in terms of weight-appropriate dose, number of administrations per day and patient age. Furthermore, in 31.4% of the cases, NSAIDs were taken without any medical prescription. These findings reinforce the hypothesis that at least in a subset of patients, NSAIDs GI toxicity is related to improper use rather than the safety profile of the molecules.

The main indications for NSAID use was pain and fever, confirming the increasing tendency to prescribe NSAIDs, and mainly ibuprofen, for their antipyretic properties. It is generally assumed that gastrointestinal bleeding is associated with long-term use of NSAIDs[1]. However, in our study, the median time between NSAIDs use and GI bleeding was 4 d, highlighting that the adverse event may occur even during short-term therapy. Hematemesis was the most frequent symptom, being present in 33.3% of the patients included in the study. In addition, this manifestation seems age-related, being significantly more frequent among younger children. This data could in someway be linked to the location of the lesions. Indeed, children of the youngest age group (⩽ 3 years), showed more proximal lesions (esophagus and stomach) compared with the oldest age group (mainly duodenal lesions). Grimaldi-Bensouda *et al*[13] reported similar data, with esophageal lesions being more frequent in younger children.

Although data in pediatrics are still limited, according to the American College of Gastroenterology, the main risk factors for NSAID-related GI toxicity should be considered: the concomitant use of other medications (including corticosteroids, anticoagulants, antiplatelet), a history of previous peptic ulcer, *H. pylori* infection, prolonged or high-dose therapy[1]. In relation to these factors, certain groups of patients at greater risk may be identified and an adequate preventive strategy may be used[1]. Risk stratification does not seem to be translated in pediatric patients. Indeed, a high number of our patients showed significant risk factors for bleeding, including comorbidities, family history for peptic disease and active *H. pylori* infection. Concerning the association with *H. pylori* infection, it is still unclear whether NSAIDs GI toxicity is increased in patients with *H. pylori* gastritis[20]. Some authors suggest *H. pylori* detection and eradication at least in chronic users[21]. Another main risk factor is the use of other concomitant drugs. In our study population, 29.6% of patients had taken other drugs at the same time, including steroids, antibiotics and acetaminophen. In particular, concerning the concomitant use of ibuprofen and acetaminophen, the American Academy of Pediatrics strongly discourages the therapeutic association, due to the low benefit/risk ratio[22]. The most common prevention strategies consist of the use of gastro-protective drugs. In our study population, 9.8% of enrolled patients used gastro-protective agents, and their use was significantly associated with duration of therapy and number of administrations, suggesting that prevention strategy is currently adopted only for longer courses of treatment.

This study has several limitations. Besides the retrospective nature and therefore the possibility of recall biases, our study was mainly descriptive, since we did not have any comparison groups to draw definitive conclusions regarding overall NSAIDs safety.

This survey represents the first Italian retrospective study on pediatric population to describe GI bleeding secondary to the use of NSAIDs. These data show that the risk of adverse events seems to be related to their improper use rather than to NSAIDs safety profile. The high number of self-prescriptions and the high percentage of inappropriate use represent the most alarming data. These findings underline the need for better promotion of NSAIDs use in children among general pediatricians and families, in order to prevent the occurrence of serious adverse events. Further studies are needed to better define possible risk stratification and preventive strategies in pediatric patients.

COMMENTS

Background

Use of non-steroidal anti-inflammatory drug (NSAIDs) has emerged as the most important cause of peptic ulcer bleeding worldwide. This is also evident in pediatric population. A number of factors are known to increase the risk of ulcer bleeding with NSAID, including comorbid disease, young age and use of high-dose of multiple NSAIDs.

Research frontiers

The most important area in the clinical study in this field is related to the high risk of gastrointestinal bleeding in pediatric population when there is poor adherence to the indications and dosages of NSAID. An adequate knowledge of these risks is helpful as a precautionary measure.

Innovations and breakthroughs

This is one of the few retrospective studies conducted in the pediatric population that defines clinical presentation, type and distribution of lesions of the gastrointestinal tract secondary to the use of NSAID.

Applications

The results of this survey can change the manner of use of these drugs in clinical practice.

Peer-review

This study confirms a three-fold increased risk of upper gastrointestinal complications associated with NSAID use. Data in elderly population are known, while there are few studies in the pediatric population. An adequate prevention can be useful to limit the risks of important side effects.

REFERENCES

1 **Lanza FL**, Chan FK, Quigley EM. Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastroenterol* 2009; **104**: 728-738 [PMID: 19240698 DOI: 10.1038/ajg.2009.115]

2 **Dills R**, Anderson LA, Pierce CA. The role of nonsteroidal anti-inflammatory drugs in pediatric patients. *Pharmacol Res* 2012; **65**: 5-8 [PMID: 21924358 DOI: 10.1016/j.phrs.2011.08.010]

3 **Singh G**. Gastrointestinal complications of prescription and over-the-counter nonsteroidal anti-inflammatory drugs: a view from the ARAMIS database. Arthritis, Rheumatism, and Aging Medical Information System. *Am J Ther* 2000; **7**: 115-121 [PMID: 11319579]

4 **Singh G**, Triadafilopoulos G. Epidemiology of NSAID induced gastrointestinal complications. *J Rheumatol Suppl* 1999; **56**: 18-24 [PMID: 10225536]

5 **Wolfe MM**, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med* 1999; **340**: 1888-1899 [PMID: 10369853]

6 **Matsui H**, Shimokawa O, Kaneko T, Nagano Y, Rai K, Hyodo I. The pathophysiology of non-steroidal anti-inflammatory drug (NSAID)-induced mucosal injuries in stomach and small intestine. *J Clin Biochem Nutr* 2011; **48**: 107-111 [PMID: 21373261 DOI: 10.3164/jcbn.10-79]

7 **Etienney I**, Beaugerie L, Viboud C, Flahault A. Non-steroidal anti-inflammatory drugs as a risk factor for acute diarrhoea: a case crossover study. *Gut* 2003; **52**: 260-263 [PMID: 12524410]

8 **Berezin SH**, Bostwick HE, Halata MS, Feerick J, Newman LJ, Medow MS. Gastrointestinal bleeding in children following ingestion of low-dose ibuprofen. *J Pediatr Gastroenterol Nutr* 2007; **44**: 506-508 [PMID: 17414151]

9 **Titchen T**, Cranswick N, Beggs S. Adverse drug reactions to nonsteroidal anti-inflammatory drugs, COX-2 inhibitors and paracetamol in a paediatric hospital. *Br J Clin Pharmacol* 2005; **59**: 718-723 [PMID: 15948937]

10 **Autret-Leca E**, Bensouda-Grimaldi L, Maurage C, Jonville-Bera AP. Upper gastrointestinal complications associated with NSAIDs in children. *Therapie* 2007; **62**: 173-176 [PMID: 17582320]

11 **Clarkson A**, Choonara I. Surveillance for fatal suspected adverse drug reactions in the UK. *Arch Dis Child* 2002; **87**: 462-466 [PMID: 12456539]

12 **Mulberg AE**, Linz C, Bern E, Tucker L, Verhave M, Grand RJ. Identification of nonsteroidal antiinflammatory drug-induced

gastroduodenal injury in children with juvenile rheumatoid arthritis. *J Pediatr* 1993; **122**: 647-649 [PMID: 8463919]

13 **Grimaldi-Bensouda L**, Abenhaim L, Michaud L, Mouterde O, Jonville-Béra AP, Giraudeau B, David B, Autret-Leca E. Clinical features and risk factors for upper gastrointestinal bleeding in children: a case-crossover study. *Eur J Clin Pharmacol* 2010; **66**: 831-837 [PMID: 20473658 DOI: 10.1007/s00228-010-0832-3]

14 **Lundell LR**, Dent J, Bennett JR, Blum AL, Armstrong D, Galmiche JP, Johnson F, Hongo M, Richter JE, Spechler SJ, Tytgat GN, Wallin L. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut* 1999; **45**: 172-180 [PMID: 10403727]

15 **Forrest JA**, Finlayson ND, Shearman DJ. Endoscopy in gastrointestinal bleeding. *Lancet* 1974; **2**: 394-397 [PMID: 4136718]

16 **Bianciotto M**, Chiappini E, Raffaldi I, Gabiano C, Tovo PA, Sollai S, de Martino M, Mannelli F, Tipo V, Da Cas R, Traversa G, Menniti-Ippolito F; Italian Multicenter Study Group for Drug and Vaccine Safety in Children. Italian Multicenter Study Group for Drug and Vaccine Safety in. Drug use and upper gastrointestinal complications in children: a case-control study. *Arch Dis Child* 2013; **98**: 218-221 [PMID: 23264432 DOI: 10.1136/archdischild-2012-302100]

17 Recommendations by the paediatric working group of AIFA (Italian Drug Agency) on the use of NSAIDs in children (2010). Available from: URL: http://www.agenziafarmaco.gov.it/sites/default/files/fans__raccomandazione_wgp_23112010.pdf

18 **Lesko SM**, Mitchell AA. An assessment of the safety of pediatric ibuprofen. A practitioner-based randomized clinical trial. *JAMA* 1995; **273**: 929-933 [PMID: 7884951]

19 **Lesko SM**, Mitchell AA. The safety of acetaminophen and ibuprofen among children younger than two years old. *Pediatrics* 1999; **104**: e39 [PMID: 10506264]

20 **Boukthir S**, Mazigh SM, Kalach N, Bouyahya O, Sammoud A. The effect of non-steroidal anti-inflammatory drugs and Helicobacter pylori infection on the gastric mucosa in children with upper gastrointestinal bleeding. *Pediatr Surg Int* 2010; **26**: 227-230 [PMID: 19823852 DOI: 10.1007/s00383-009-2492-x]

21 **Chan FK**, Ching JY, Suen BY, Tse YK, Wu JC, Sung JJ. Effects of Helicobacter pylori infection on long-term risk of peptic ulcer bleeding in low-dose aspirin users. *Gastroenterology* 2013; **144**: 528-535 [PMID: 23333655 DOI: 10.1053/j.gastro.2012.12.038]

22 **Sullivan JE**, Farrar HC, Section on Clinical Pharmacology and Therapeutics; Committee on Drugs. Fever and antipyretic use in children. *Pediatrics* 2011; **127**: 580-587 [PMID: 21357332 DOI: 10.1542/peds.2010-3852]

P- Reviewer: Grizzi F, Kapan S, Yucel O **S- Editor**: Ma YJ
L- Editor: Ma JY **E- Editor**: Wang CH

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327