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Endoscopic findings in children on non-steroidal anti-inflammatory drugs (NSAIDs)

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Abstract

Background: Non-steroidal anti-inflammatory drugs (NSAIDs) remain as the initial approach to the pharmacologic management in juvenile rheumatoid arthritis (JRA). Gastrointestinal (GI) damage associated with NSAIDs is common in adults, but there are few studies available in children. This study was performed to determine the GI complications due to the use of NSAIDs in a cohort of JRA patients by endoscopy.

Methods: Twenty-one patients with JRA who were using NSAIDs for at least 3 months were assessed clinically and by endoscopy at Pediatric Immunology Clinic of Nemazee Hospital affiliated to Shiraz University of Medical Sciences in Shiraz, southern Iran from June 1999 to June 2003..

Results: The mean age of the patients was 9.8 years (11 females), and the mean duration under NSAIDs management was 16 months. The most common NSAIDs used was diclofenac. GI symptoms were found in 42.9% of patients including 33.4% abdominal pain and 9.5% vomiting. There was no significant difference between the patients and symptoms free subjects in regard to mean duration of treatment. Macroscopic endoscopic lesions were found in 85.7% and infection of Helicobacter pylori (Hp) in 14.3% of cases. There was no significant relationship between endoscopic findings and duration of treatment or clinical symptoms.

Conclusions: Our data showed that patients using NSAIDs had frequent GI damage without any relationship to the duration of treatment. There were also a high number of children with GI damage and without any clinical complaint. Furthermore, we found no significant relationship between the duration of drug use and the GI complaints, and no relation between duration and GI complaints to upper GI tract endoscopic lesions. The possibility of GI derangements with NSAIDs in pediatric age group is high. Close monitoring of symptoms and prevention measures are suggested.

Keywords: Endoscopic findings; Children; Non-steroidal anti-inflammatory drugs

Introduction

Currently the non-steroidal anti-inflammatory drugs (NSAIDs) are the first line medications in the treatment of patients with inflammatory arthritis, muscuoskeletal pain, biliary and urinary colic, and dysmenorrhea. The most common side effects of these drugs are abdominal discomforts and gastrointestinal (GI) derangements. Secondary peptic ulcer disease (PUD) following the use of NSAIDs is common and the risk of PUD in adults increases 3 to 5-folds with up to 35% of the PUD in adults being due to the use of such medications.[1-6] Currently, because of limited research on the use of these drugs in the field of pediatric,[7] the present study was undertaken to evaluate all children receiving NSAIDs for at least 3 months, and referring to the outpatient clinic of pediatric immunology and gastroenterology for the digestive system side effects and endoscopy findings.

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Materials and Methods

The present study was performed to evaluate clinical and endoscopic findings of GI damage in 38 patients,

already on NSAIDs for at least 3 months, referred to the Pediatric Immunology Clinic of Nemazee Hospital affiliated to Shiraz University of Medical Sciences in Shiraz, southern Iran from June 1999 to June 2003. All patients were randomly selected, had juvenile rheumatoid arthritis (JRA) according to the American College of Rheumatology (ACR) criteria and were on NSAIDs for at least 3 months. The selection of patients was not based on any particular drug among the NSAIDs or the presence or absence of GI symptoms. Inclusion criteria were definitive disease diagnosis and ensuring the patients' regular use of drug. A semi-standard questionnaire was prepared for each patient that provided information on age, gender, disease presentation, duration of the disease, type, daily dose and duration of the NSAID used, and any co-administered drugs. Having been confirmed by a pediatric immunologist, each patient was referred to the pediatric gastroenterologist who re-evaluated any clinical manifestation of GI diseases. A further questionnaire recording any previous PUD, vomiting, GI bleeding, heartburn, and family history of PUD in first-degree relatives was then completed for each patient. Patients were subsequently subjected to endoscopic evaluation after obtaining a written consent from their parents. Endoscopic findings, separately recorded for each case, included erythema, erosions, nodularity, and ulceration in any part of the upper GI tract. In all patients biopsy was obtained from normal and abnormal looking mucosa of the esophagus, stomach and duodenum and sent for histopathologic examination. The patients were also explored for Helicobacter pylori (Hp) infection by urease test and if positive the appropriate treatment was instituted.

Some patients lived far from Shiraz and because of the lengthy waiting period between clinical examination and availability of endoscopy results, 12 patients did not turn up for endoscopy. Despite an active door-to-door screening and follow-up of patient's clinical records, five patients who had been selected for the study, could not be followed, and only 21 patients completed the study.

Whenever applicable, the data obtained were analyzed by Mann-Whitney and Chi-Square tests. A larger part of the study was otherwise descriptive.

Results

Of 21 patients, 11 (52.3%) were female and 10 (47.6%) were male, giving a female to male ratio of 1.1. The patients aged from 2-14 years with a mean of 9.8 years. The shortest period for NSAIDs treatment was 3 months, and the longest was 8 years, with a mean duration of 16 months. The most frequently used NSAIDs was diclofenac, with 12 patients (57.1%) and the least prescribed was indomethacin with 1 patients (4.7%). Other drugs included naproxen, iboprufen, and aspirin with 3, 3, and 2 cases, respectively. In one case, the patient received one dose of tolmetin and then switched to naproxen during the course of study, while another was treated with a combination of aspirin and diclofenac. In 12 cases, patients were on concurrent medications, including methotrexate, sulfasalazine and prednisolone. A total of 12 cases (57.1%) were symptom free, and epigastric pain and vomiting were found in 7 (33.4%) and 2 (9.5%) patients respectively. Only one patient had a family history of PUD, and the rest had no familial PUD or GI bleeding. On endoscopy, 3 patients (14.3%) were normal, while 18 (85.7%) exhibited abnormalities. Erythema, erosions and nodularity are shown in Table 1. Interestingly, at least 2 of these entities were simultaneously present in some cases with no ulcer detected in any of the patients. Three patients (14.3%) tested positive for Hp infection while 18 patients (85.7%) tested negative. There was no significant relationship found between the mean age of patients with clinical symptoms and symptom free cases (p=0.9). Similarly, no significant difference was observed between symptomatic and asymptomatic patients in regard to the mean duration of treatment (P=0.7). For the sake of convenience, of nodularity and erythema, only the latter was taken into account as a distinguishing factor. In this regard, there was no significant relationship between the duration of treatment and endoscopic findings, despite that all patients had been on NSAIDs for at least 3 months (P=0.8). In the patients with erythema (n=15), 7 were symptomatic (epigastric pain, vomiting) whereas 8 were symptom free, while, among patients without erythema (n=6), 2 patients had clinical symptoms and 4 cases were asymptomatic. Thus there was no relationship between clinical symptoms and endoscopic findings (P=0.6).

Discussion

Studies are limited worldwide and involve crude diagnostic capabilities of used equipments or the small sample size, which led to different shortfalls. Our

Table 1: General information of patients under study

No.	Gender	Age (years)	Duration of Drug Use	Drug Used	Daily Dose	Drugs Used combined with NSAIDs	Clinical Finding	Endo-scopic Finding	Infection with *H. pylori*	Control Group	
1	F	11	12 mo	Nap	750	MTX-SLZ-Pred	NL	Eso	-	-	+
2	M	9	1.5 yrs	Dic	75	MTX	Abd pain	Eso, Gas, Duo	-	-	-
3	M	10	3.5 mo	Dic	50	-	Abd pain	Gas, Duo	+	-	-
4	F	13	9 mo	ASA	600	-	NL	Gas	-	+	+
5	F	10	4.5 yrs	Dic	50	MTX-SLZ	NL	Gas, Duo	-	-	+
6	F	9	2 yrs	Dic	50	MTX	Vom	Gas	-	+	-
7	F	7	8 mo	Bruf	1200	MTX	Abd pain	Gas	-	-	-
8	F	12	1 yr	Bruf	1200	MTX-Pred	NL	Gas	-	+	+
9	F	9	4 mo	Dic	50	-	NL	Gas, Duo	-	-	+
10	F	8	2 yrs	Dic	75	-	NL	Gas	+	+	+
11	F	7	1 yrs	Dic	25	-	NL	NL	-		
12	M	2	3 mo	ASA	600	-	NL	NL	-	-	+
13	M	12	10 mo	Bruf	800	MTX-SLZ	NL	Gas, Duo	-	-	-
14	M	4	9 mo	Nap	500	MTX-SLZ	NL	NL	-	-	+
15	F	10	8 yrs	Ind	50	-	Abd pain	Eso, Gas	-	-	-
16	M	10	3.5 mo	Dic	75	Pred	Vom	Gas	-	-	+
17	M	12	9 mo	Dic	75	SLZ	NL	Eso, Gas	-	+	+
18	F	14	2 yrs	Dic	75	-	Abd pain	Duo	-	+	+
19	M	14	8 mo	Dic	75	-	NL	Gas	+	-	-
20	M	11	12 mo	Nap	750	Pred	Abd pain	Eso	-	-	-
21	M	11	5 mo	Dic, ASA	50, 100	MTX	Abd pain	Eso, Gas, Duo	-	-	-

Dic:diclofenac, Nap: naproxen, Ind: indomethacin, Bruf: brufen, MTX: methotraxate, SLZ:sulfasalazin, Pred: prednisolone, Eso: esophagitis, Gas: gastritis, Duo: duodenitis, Abd: abdominal, NL: normal, M: male, F: female

study is unique in that it involved a larger sample, and was conducted prospectively. Despite endoscopic findings, 42.9% of cases in our study had no clinical symptoms of GI disease. This indicated that clinical signs and symptoms of GI disorders alone were not sufficiently reliable to confirm or refute the presence of mucosal damage in patients on NSAIDs. In one study, 27% of children with endoscopic findings had no clinical manifestations,[8] and according to another report, adults on long term treatment with NSAIDs and evaluated by endoscopy had no clinical signs or symptoms. However, 76% and 27% of these patients had damages of the gastric and duodenal mucosa, respectively.[9] This has also been reported in several independent studies.[10,11] The mechanism of NSAIDs action has not yet been elucidated.

It is probable that with suppression of pain by inhibiting prostaglandin synthesis, thereby, the ability of lesions to elicit pain, NSAIDs totally suppresses the classic manifestations of mucosal damage. Further studies are thus needed to attest to the plausibility of this hypothesis. In accord with the results of another study,[12] 76% of our cases suffered from damage to the gastric and/or duodenal mucosa. There was no peptic ulcer detected in any of our patients. This was in contrast to the results of foregoing study in which endoscopy was performed on patients presenting with abdominal pain, hematemesis, melena, or iron deficiency anemia. In other words, the evaluation of the patients coincided with severe clinical GI side effects of NSAIDs. In fact, in one study it was reported that there was a direct relationship between iron deficiency anemia and endoscopic lesions in patients on NSAIDs.[8] The type of mucosal damage found in 71.4% of our cases was erythema of gastric antrum, a similar finding to a study performed in adults.[4]

However, a novel finding in our study was the higher incidence of erythema in the esophagus (28.5%) compared to that of the duodenum (23.8%). This was despite similarity between our study and other investigations in regard to pathological findings of gastric and duodenum. Our study showed no relationship between

the age of patients on NSAIDs and the presence and absence of symptoms. Additionally, there was no significant difference in the mean duration of treatment between symptomatic and symptom free patients. The finding that 3 patients (No. 3,16,21) were on NSAIDs for 3-5 months before developing GI symptoms was unrelated to the concurrent use of NSAIDs with other drugs. This was confirmed by patients (1,5,8,10) on NSAIDs for 1-2 years whose conditions were not deteriorated any furthur.

There was also no difference found between symptomtic and asymptomatic patients in connection with concurrent use of other medications. As seen, 6 patients (No. 1,5,8,13,14,17) who used concurrent medications had no symptoms, while 6 patients (No. 2,6,7,16,20,21) who only received NSAIDs were symptomatic. The presence or absence of clinical signs is not an indication of mucosal damage in patients on NSAIDs as among the patients with erythema, there was no significant relationship found between patients with clinical symptoms and asymptomatic cases. The most widely used drug in our study was diclofenac, although on closer inspection, it was revealed that with regard to naproxen and ibuprofen, the former was relatively safer. Three patients (No. 1,14,20) suffered from esophagitis while on naproxen compared to the patients on ibuprofen (No. 7,8,3) who developed gastritis. Based on the results of our study, it was speculated that in connection with damage to GI mucosa, treatment with naproxen was safer than other routine NSAIDs. This study also revealed that simultaneous use of two NSAIDs is an additive risk factor. The only case in our study with both clinical signs and severe endoscopic findings was patient (No. 21). Finally in our study, the prevalence of the Hp infection in patients on NSAIDs was 14.3%, in contrast to 57.2% reported in similar studies.[8,13,14]

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