Incidence of Aspirin-Related Hepatotoxicity in Pediatric Cases with Acute Rheumatic Fever

Olgun H., Bulgan M., Ceviz N., Yolcu C., Sahin I. O., Laloglu F.
Atatürk University, Faculty of Medicine, Department of Pediatrics, Division of Pediatric Cardiology, Erzurum, Turkey.

INTRODUCTION

Acute rheumatic fever (ARF) is a multisystem inflammatory disease that remains a serious healthcare concern for the majority of the world's population, particularly in the developing countries. Anti-inflammatory agents, namely salicylates and corticosteroids, remain the first-line agents in the treatment of rheumatic fever and usually provide dramatic clinical improvement. Liver function tests, including serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity, can be negatively affected in children receiving anti-inflammatory doses of aspirin. This study aims to investigate the incidence of hepatotoxicity in pediatric patients who were diagnosed with ARF and received aspirin treatment.

PATIENTS & METHODS

Acute rheumatic fever was diagnosed according to modified Jones criteria that modified by AHA in 1992 and 2003. Pediatric patients, who were diagnosed with ARF between January 2008 and August 2015, were retrospectively analyzed. Patients whose initial attacks were diagnosed before 2008, patients whose diagnosis was uncertain, patients with known systemic diseases (except for rheumatic heart disease), patients who were continuously used drugs for another reason that elevates the liver enzymes were excluded. In our clinic, we have an anti-inflammatory treatment protocol for patients with ARF as following: prednisolone is given to patients with moderate-to-severe carditis for two weeks. At the end of the second week, the prednisolone is gradually reduced and discontinued. When steroid therapy is begun to discontinued, acetylsalicylic acid (80-100 mg/kg/day, maximum 3.5 g/day) is started and continued for 6-8 weeks. Acetylsalicylic acid (80-100 mg/kg/day, maximum 3.5 g/day) is being administered to the patients with isolated arthritis and/or mild carditis, treatment is continued for 4-6 weeks. Liver enzyme (AST, ALT, LDH, GGT, ALP) levels are evaluated before to and on 3rd, 7th, 15th and 30th days of the treatment. Clinical findings (i.e. nausea and vomiting) of aspirin related hepatotoxicity are also questioned daily before and during the treatment. Patient's parents are informed about the signs of aspirin toxicity before the discharge. In case of newly developed symptoms, patients were reevaluated.

Patients who had more than one ARF episodes were assessed separately for each aspirin treatment during the attack. Therefore, 281 ARF attacks in 258 patients were included in this study. Presence of hepatotoxicity related clinical symptoms (nausea, vomiting,) and at least a twofold increase in liver enzymes, compared to reference values,was accepted as symptomatic hepatotoxicity. In case of a two-fold or more increase in liver enzymes but no clinical symptoms it was accepted as asymptomatic hepatotoxicity. Aspirin doses were reduced in patients who developed asymptomatic hepatotoxicity (60-65 mg/kg/day). Liver enzymes and clinical signs were evaluated on a daily basis. In patients with liver enzymes are in the trend of normalization, anti-inflammatory treatment was completed with aspirin. Aspirin was discontinued in patients with symptomatic hepatotoxicity and in patients with asymptomatic hepatotoxicity findings who had markedly elevated liver enzymes and/or newly developed clinical manifestations of hepatotoxicity. Other anti-inflammatory drugs (naproxen sodium or ibuprofen) or steroids were initiated according to the clinical status of patients who did not take aspirin treatment for a sufficient period of time.

Aspirin group was also divided into two subgroups including those who developed hepatotoxicity and did not. These patients were also classified according to whether they were symptomatic or not. The patients in the hepatotoxic group were divided to subgroups according to the type of treatment modification; a) aspirin is reduced and the treatment is completed with aspirin, b) aspirin is discontinued and the treatment is completed with naproxen sodium, c) aspirin is discontinued and the treatment is completed with ibuprofen, d) aspirin is discontinued and treatment is completed with steroids, e) aspirin was started during the cessation period of steroid treatment and the treatment was completed with naproxen sodium because of hepatotoxicity; f) aspirin was started during the cessation period of steroid treatment and treatment is completed with steroids because of hepatotoxicity.

Aspirin-related side effects were examined based on the doses and body weight. Incidence of hepatotoxicity was investigated in these groups. Total aspirin doses, aspirin dose per kilogram of weight, day of hepatotoxicity, and normalization times of liver enzymes were detected. It was also noted whether the hepatotoxicity was symptomatic or asymptomatic.

Demographic data (age, gender), major, minor clinical and laboratory parameters that may have an impact on the development of aspirin-related hepatotoxicity were analyzed. In patients with hepatotoxicity, the laboratory response to reducing the dose of aspirin or cessation of aspirin and initiating NSAIDs or steroids was evaluated.

Patients were grouped in terms of body weight as; between 25-34 kg, and ≥ 35 kg. Also they were grouped in terms of aspirin dose as; lower than 65 mg/kg/day or ≥65 mg/kg/day. Hepatotoxicity frequency was investigated in these groups.

RESULTS

A total of 258 patients (281 attacks) diagnosed as ARF between July 2008 and August 2015 was included in this study. Of 258 patients 112 (43.4%) were male. A total of 237 patients were seen during one episode (84.3%) and 21 patients during at least two episodes (44 episodes in total). The recurrence rate was 8.2% (23/281). Some patients (84 patients, 86 attacks) either did not receive anti-inflammatory treatment (76 patients, 78 attacks), or received drugs other than aspirin (8 patients, 8 attacks). For these eight patients (8 attacks) aspirin treatment would be thought to be harmful due to newly developed varicella zoster (n = 1), newly developed zona zoster (n = 1), high transaminase level at diagnosis (n = 2), irregular steroid usage (n=1), undetermined causes (n = 3). So naproxen sodium was given.

The data of the remaining 174 patients with 195 episodes of ARF were the main content of this study. When the patients with ARA were evaluated according to age at diagnosis the majority of the patients were between 9 and 15 years of age (Figure 1). The most common major finding was carditis (73%). This was followed by polyarthritis (66.9%) and Sydenham cores (30.6%). The least common major finding was subcutaneous nodules (0.4%) and no patient had erythema marginatum (Table 1). During 166 of the episodes patients had mild carditis and/or arthritis and aspirin was given as the first line drug. Whereas aspirin was added when the steroid was decreased in twenty-nine patients, as they had moderate-to-severe carditis or significant valve involvement.

Findings of patients who received aspirin, and analysis of effective parameters on hepatotoxicity

Clinical parameters that were examined whether they had or not any effects on hepatotoxicity development are given in Table 2. Frequency of arthritis was significantly higher among patients with hepatotoxicity (p = 0.037).

Comparison of the demographic data and laboratory parameters in terms of presence of hepatotoxicity is given in Table 3. There was no significant difference between the groups in terms of mean age, body weight, aspirin dose, and total aspirin amount, and ASO, CRP and ESR levels (Table 3).

To investigate the effect of aspirin doses on hepatotoxicity frequency, Patients were grouped in terms of body weight as less than 25 kg and ≥25 kg. Average aspirin doses were 99.7±2.9 mg/kg and 82.3±18.1 mg/kg, respectively. The mean aspirin dose was significantly higher in patients with a body weight below 25 kg (P = 0.000). However, there was no significant difference in the incidence of hepatotoxicity among patients with body weight above or below 25 kg (31.8% and 29.1%, respectively, p = 0.840). Similarly, when patients were grouped below and above the body weight of 35 kg, there was no difference in mean aspirin doses among the groups and there was no difference in hepatotoxicity frequency (t = 0.295; p = 0.768). In addition, to determine the effect of aspirin dose of 60-70 mg/kg/day, known as the minimum anti-inflammatory dose for aspirin, patients were divided into two groups in terms of aspirin doses of less than 65 mg/kg/day or above. The mean aspirin doses were 56.1±7.5 mg/kg and 89.7±11.6 mg/kg respectively, and difference was statistically significant (p = 0.005). However, there was no significant difference in the incidence of hepatotoxicity between the two groups (9.1% and 20.7%, respectively, p = 0.156). Figure 2 shows mean AST and ALT levels during aspirin therapy. Figure 3 shows mean LDH levels during aspirin therapy. Figure 3 and 4 show mean LDH and ALP levels during aspirin therapy respectively.

Analysis of patients with hepatotoxicity

In 83 of 195 (42%) episodes hepatotoxicity developed. Patients were symptomatic (nausea, vomiting) in 36 (43.4%). However, the remaining 47 patients (56.6%) were asymptomatic (isolated liver enzyme elevation). Among whole study group (n=195) the frequency of symptomatic hepatotoxicity was found to be 18.5% and the asymptomatic hepatotoxicity was found to be 24.1%.

Gastrointestinal symptoms such as nausea and/or vomiting were present in symptomatic (n=36) patients and tinnitus was seen in only five (12.2%) episodes. All patients responded to treatment changes and the findings of hepatotoxicity disappeared. Death and permanent organ damage was not observed.

Some patients with clinical and laboratory findings of hepatotoxicity were screened to exclude other liver diseases (viral serology, coagulation factors). In this context, EBV viral capsid antigen Ig M was positive in a patient, and the patient was evaluated as EBV hepatitis. Elevated INR values were present in five patients with high liver function tests. Two of them were receiving warfarin due to previous valve replacement. One patient was diagnosed with Factor 7 deficiency on follow-up. In remaining two it was thought to be as a result of aspirin hepatotoxicity.

Hepatotoxicity symptoms appeared in a mean time of 14.7±10.6 days (3-51 days) after the initiation of aspirin (table 4). Hepatotoxicity was detected in 15.1±12.2 days in symptomatic attacks and 14.4±9.3 days in asymptomatic patients. The mean first detection days of symptomatic and asymptomatic hepatotoxicity was similar (p = 0.751).

The distribution of the normalization times of elevated liver enzymes in patients who developed hepatotoxicity is given in table 5. Elevated liver enzymes returned to normal reference values at mean 16.1 ± 11.2 days (range 2-68 days). This period was 16±13.3 days in symptomatic patients and 16.1 ± 9.3 days in asymptomatic patients. The difference was not statistically significant (p = 0.970)

Duration of normalization of liver function tests in different anti-inflammatory treatment protocols

Mean normalization time of high liver functions in patients with hepatotoxicity is given in table 6. Aspirin had been started in one patient but treatment was changed to ibuprofen when hepatotoxicity developed. This patient is not account into consideration in statistical analysis. No significant difference was detected in the mean normalization duration of high liver functions (f=1,173, p=0,325)

Table 1. Distribution of major manifestations of acute rheumatic fever at every attack

Major finding	n	%
Carditis	205	73.0
Poliarthritis	188	66.9
Sydenham chorea	86	30.6
Subcutaneous nodule	1	0.4
Erythema marginatum	0	0

Table 2. Analysis of possible clinical parameters for effect on hepatotoxicity development

		HT(-) (n=112)		HT(+) (n=83)		x^2	p
		N	%	N	%		
Gender	Male	57	50.9%	35	42.2%	x^2=1.456	p=0.144
	Female	55	49.1%	48	57.8%		
Positive throat culture		24	21.4%	26	31.3%	x^2=2.449	p=0.081
Arthralgia		24	21.4%	23	27.7%	x^2=1.029	p=0.199
Arthritis		99	88.4%	80	96.4%	x^2=4.043	p=0.037
Carditis		108	96.4%	81	97.6%	x^2=0.216	p=0.491
Sydenham chorea		6	5.4%	3	3.6%	x^2=0.329	p=0.417

HT: hepatotoxicity

Table 3. Mean values of some clinical and laboratory parameters in terms of hepatotoxicity

	HT(-) (n=112) Mean±SD	HT(+) (n=83) Mean±SD	t	p
Age	12.1±2.8	11.4±2.2	1.673	0.096
Body Weight (kg)	39.2±13.6	38.6±11.8	0.295	0.768
Aspirin doses (mg/kg)	85.4±16.1	86.2±15	0.365	0.716
Total aspirin (gram)	3.1±0.5	3.17±0.5	0.292	0.771
ASO (IU/L)	986.4±456.3	1076.6±534.2	1.268	0.206
ESR (mm/saat)	62.3±30.8	70.2±28.4	1.814	0.071
CRP (mg/dl)	41±47.6	38.7±39.3	0.354	0.724

HT: Hepatotoxicity

Table 4. The times and rates of hepatotoxicity in symptomatic and asymptomatic children

	Symptomatic patients		Asymptomatic patients	
	N	%	n	%
1-3th day	3	3.6	3	3.6
4-7th day	14	16.9	14	16.9
8-15th day	9	10.9	17	20.5
16-30th day	7	8.4	11	13.2
Day 31th and over	3	3.6	2	2.4

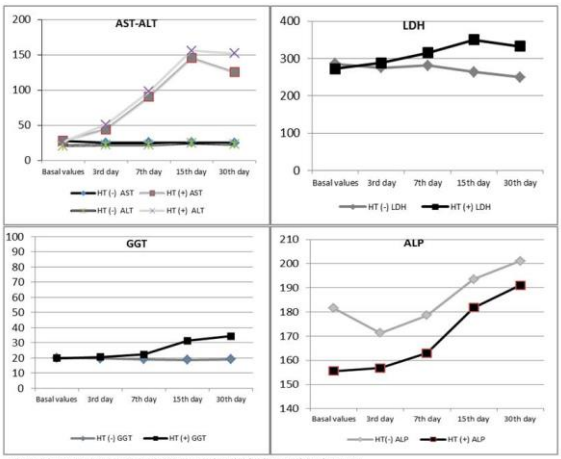

Figure 1. Mean AST, ALT, LDH, GGT, ALP levels during aspirin therapy
HT: Hepatotoxicity

Table 5. Normalization times of liver enzymes in symptomatic and asymptomatic children

	Symptomatic patients		Asymptomatic patients	
	n	%	n	%
1-3th day	2	3.4	1	1.2
4-7th day	6	7.2	7	8.4
8-15th day	15	18	21	25.3
16-30th	8	9.6	15	18
Day 31th and over	5	6	3	3.6

Table 6. Patient numbers and the mean normalization times of liver enzymes of patients who had hepatotoxicity and who underwent treatment changes

Treatment changes	n	%	Mean normalization times of liver enzymes
Aspirin is reduced and the treatment is completed with aspirin	24	28.9	16.4 ± 10.3
Aspirin is discontinued and the treatment is completed with naproxen sodium	24	28.9	12.8 ± 10.5
Aspirin was started during the cessation period of steroid treatment			
1. and the treatment was completed with naproxen sodium	14	14.4	11.9±6
1. and aspirin is discontuined and the treatment is completed with steroid	21	25.3	16.6 ±13.3
			F=1.173, p=0.325

Conclusion:

- ***Hepatotoxicity is common in the ARF patients receiving aspirin.***
- ***As most of these patients have no symptoms, they should be evaluated for liver enzymes on a regular basis.***
- ***Reduction of the dose of aspirin or treatment modification with a new anti-inflammatory drug seems as effective as aspirin.***
- ***Effects of the other NSAIDs on ARF treatment that known to have lesser side effects on liver should be evaluated by new studies.***