OLGU SUNUMU

ACUTE NONOLIGURIC RENAL FAILURE ASSOCIATED WITH NAPROXEN SODIUM IN A CHILD

ÇOCUKTA NAPROKSEN SODYUM KULLANIMINA BAĞLI
AKUT NONOLİGURİK BÖBREK YETMEZLİĞİ

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SUMMARY

Non-steroidal anti-inflammatory drug (NSAID) associated nephrotoxicity is uncommon during childhood in contrast to higher incidence in adults.

A 12-year-old previously healthy boy was admitted to hospital with abdominal pain after ingestion of 275 mg of Naproxen bid for three days to relieve toothache. His physical examination was within normal limits except dental caries at left first premolar tooth. Erythrocyte sedimentation rate was 65 mm/hour and urine analysis showed (+) proteinuria and 8-10 erythrocytes with normal blood biochemistry. At fifth day of admission, his urea and creatinine levels increased to 85 mg/dL and 4 mg/dL, respectively. Consecutively, he developed persistent microscopic hematuria and proteinuria of 12 mg/m^2/hour. During his hospitalization, blood pressure remained stable and urine output was normal. A renal ultrasound demonstrated increased echogenicity of kidneys and percutaneous renal biopsy revealed tubulointerstitial nephritis. He was conservatively treated with intravenous hydration and supportive care. Renal function gradually returned to normal within 14 days.

The popularity of NSAIDs continues to grow among physicians for pediatric use and many children use some form of NSAIDs on unprescribed basis. However, they can lead to severe nephrotoxicity even at therapeutic doses in healthy children. Although reported cases of naproxen induced renal failure are very few, appropriate precautions should be taken while treating children with naproxen.

Key words: Acute renal failure, naproxen use in children.

ÖZET

Anti-inflamatuvar kullanımına bağlı renal toksitite erişkin yaş grubunda sık görülmesine rağmen çocukluk yaş grubunda nadirdir.

Diş ağrısı sebebiyle 3 gün süreyle günde 2 defa 275 mg naproksen sodyum kullanan 12 yaşındaki erkek olgu karın ağrısı sebebiyle hastaneye başvurdu. Olgunun başvuru sırasında fizik bakı bulguları sol 1. premolar dişteki çürük dışında normaldi. Başlangıçta eritrosit sedimentasyon hızı 65 mm/saat, idrarda (+) protein ve mikroskopisinde ise 8-10 eritrosit dışında böbrek

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fonksiyon testleri normaldi. Yatışının 5. gününde üre 85 mg/dl, kreatinin 4 mg/dl olarak saptandı. Bu dönemde mikroskopik hematüri ve 12 mg/m^2/saat proteinüri vardı. Kan basıncı normal seyretti. İdrar çıkışı başlangıçtan itibaren yeterli olan olgunun böbrek ultrasonunda ekojenite artışı saptandı. Perkütan renal biyopside akut interstisyel nefrit saptanan hastaya intravenöz sıvı desteği uygulandı. Böbrek fonksiyon testleri 14 gün içinde aşamalı olarak normale döndü.

Çocukluk yaş grubunda kullanımı giderek artan steroid olmayan anti-inflamatuvar ilaçların tedavi dozlarında bile nefrotoksik olabileceği unutulmamalıdır. Çocuklarda naproksen kullanımına bağlı çok az sayıda olgu bildirilmiştir. Tüm steroid olmayan anti-inflamatuvar ilaçlar gibi, naproksen da çocukluk yaş grubunda dikkatli kullanılmalıdır.

Anahtar Sözcükler: Akut böbrek yetmezliği, çocukta naproksen kullanımı

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) have potentially serious side effects including kidney, skin, hematological and central nervous system but their most common side effect occurs at the gastrointestinal level. The effects of NSAIDs on the kidneys are increasingly recognized. Frequency of renal side effects was reported to range between 1-5% (1). Renal sequale include mild side effects like hyperkalemia, salt and water retention besides acute renal failure (ARF) being the most serious one. Acute hemodynamic changes and acute interstitial nephritis (AIN) are the major pathogenetic factors inducing ARF. However, underlying renal disease and dehydration increase the susceptibility to NSAID related nephrotoxicity (2). Most cases of ARF associated with NSAID usage are mild and resolve spontaneously (3).

Naproxen has similar pharmacological properties to other NSAIDs. Rheumatic diseases are the major indication for naproxen prescription during childhood in addition to treatment of inflammation and mild to moderate pain in children older than 12 years. In contrast to adults, very few pediatric cases of ARF secondary to naproxen administration have been reported (4,5). Here, we present a case of biopsy proven AIN leading to ARF induced by Naproxen at therapeutic dosage.

CASE REPORT

A 12-year-old previously healthy boy was admitted to hospital with abdominal pain after he ingested 275 mg Naproxen bid for three days to relieve his toothache. Personal and family history were unremarkable. His physical examination was normal except dental caries at left first premolar tooth. His blood pressure was approriate for age height and gender and there was neither weight gain nor edema. Initial laboratory work-up revealed whole blood count, liver enzymes, electrolytes and renal function tests as normal. Erythrocyte sedimentation rate was 65 mm/hour and urine analysis showed (+) proteinuria with 8-10 erythorcytes. Intravenous fluid of 2000 ml/m^2/day and lansoprozole of 15 mg/day were given in order to overcome renal and gastrointestinal side effects. Microscopic hematuria and proteinuria persisted. As urea and creatinine levels increased after 2 days, intravenous fluid was increased to 3000 ml/m^2/day and lansoprozole was stopped. At fifth day of admission, urea, creatinine and uric acid levels were 85 mg/dl, 4 mg/dl and 12 mg/dl, respectively (Table 1). Electrolytes, complement levels (C_3 and C_4), whole blood count, arterial blood gas and antistreptolysin O titer were normal while rheumatoid factor, dsDNA and antinuclear antibodies were negative. Abdominal pain rapidly resolved and neither abnormal physical examination findings nor hypertension were observed during follow-up. Daily urinalysis revealed proteinuria (1+), a specific gravity of 1015, nitrite negativity and 8-10 erythrocytes without eosinophiluria. Urine culture was sterile. 24-hour urine sample showed proteinuria of 10-12 mg/m^2/hour. Renal ultrasound was normal except increased echogenecity of both kidneys. Urine output was normal as 2-3 ml/kg/hour through disease course. A percutaneous kidney biopsy was performed secondary to microscopic hematuria, nephritic proteinuria and gradual deterioration of renal function.

Light microscopy of renal specimen demonstrated AIN (Figure 1). Fourteen glomeruli were observed in biopsy specimen with no sign of sclerosis and infiltration. Massive interstitial infiltration with lymphocytes, plasma cells and neutrophils was noted. The vasculature was regular in structure. Immunofluorescence examination was interpreted as normal. Starting from 7th day of intravenous hydration, renal function and urine abnormality gradually improved and totally recovered at 14th day. The patient was discharged at 15th day. At his first - and second -month visits after hospitalization, he was perfectly normal in terms of physical examination findings and laboratory results.

Table 1. Laboratory investigations during follow-up

	Day 1	Day 3	Day 5	Day 7	Day 10	Day 14
Urea (mg/dl)	18	67	85	74	55	31
Creatinine (mg/dl)	0,8	3,2	4	3,8	1,8	0,8
Uric acid (mg/dl)	5	9	12	9	5	6
Leukocyte (/mm^3)	8500	9100		10000	9500	5600
Hematocrit (%)	34	35		33	33	36
ESR*(mm/hour)	65		98		85	29
Specific gravity	1020	1015	1015	1020	1020	1015
Proteinuria(dipstick)	1+	1+	1+	1+	-	-
Urinalysis	4-5 RBC**	10-15 RBC	10-15 RBC	5-10 RBC	Normal	Normal
Proteinuria***(mg/m^2/hour)		12	10	6	4	3

*ESR: Erythrocyte sedimentation rate, **RBC: Red blood cell, ***Quantitative measurement

Table 2. Previous case reports of naproxen toxicity

Reference	Age*	Naproxen Taken for	Duration of Therapy	Extra NSAID**	Biopsy	Treatment	Outcome
3	6	Arthritis	1 week	Ø	AIN	Oral prednisolone	Recovery
4	10	JRA[§]	1 month	Diclofenak	AIN*	3 doses HDMP[+]/Oral prednisolone	Recovery
5	2	JRA	1 month	Ø	AIN	Intravenous hydration	Recovery
7	14	IBD[#]	2 months	ASA***+Tolmetin	AIN	Oral prednisolone	ESRD*
10	14	Dysmenorrhea	5 days	Rofecoxib	AIN	Intravenous hydration	Recovery
Our Case	12	Toothache	3 days	Ø	AIN	Intravenous hydration	Recovery

* Age: Years, [§]JRA: Juvenile Rheumatoid Arthritis,

** NSAID: Additional Nonsteroidal anti-inflammatory drug ingested by the patient,

*** ASA: Acetylsalicylic acid, [+]High dose methylprednisolone, [#]IBD: Inflammatory bowel disease

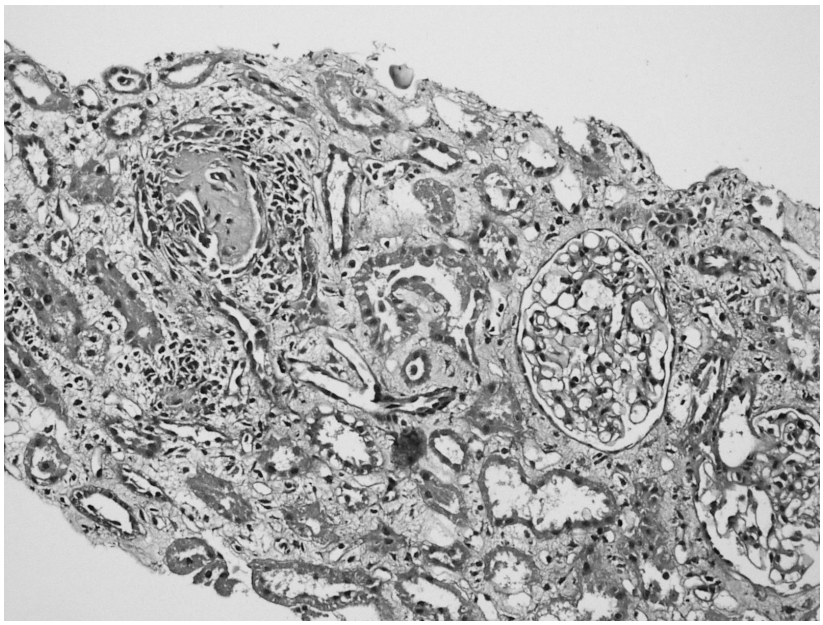

Figure 1. Tubules widely separated by interstitial edema and inflammatory infiltration composed predominantly of lymphocytes and plasma cells (Hematoxylin-eosin x 25).

DISCUSSION

We here report a 12-year-old boy who developed AIN related acute renal failure secondary to naproxen intake for toothache. We observed that the renal failure had resolved without any specific treatment except for intravenous fluids and withdrawal of naproxen.

There are two main mechanisms by which NSAID-induced kidney injury may occur: First mechanism is the hemodynamic injury secondary to inhibition of cyclooxygenase (COX) enzyme. As well known, COX produces several leukotrienes and prostaglandin molecules from arachidonnic acid, a cellular membrane lipid. Cyclooxygenase-1 (COX-1) enzyme creates prostaglandins with physiological functions like prostacyclin (PGI_2). PGI_2 is antithrombotic, protective for gastric mucosa and prevents atherosclerosis at endothelium. COX-2 on the other hand, produces cytokines leading to inflammatory response. Antiinflammatory action and side effects of NSAIDs occurs by inhibition of COX-2 and COX-1, respectively (6). Prostaglandin synthesis inhibition which has a detrimental effect on renal blood flow with consequent ARF is mediated by COX-1 inhibition.

Second mechanism of the nephropathy associated with NSAIDs use is AIN, which can lead to impairment in renal function and nephrotic syndrome or both. (3,5,7). This immune-mediated entity can present at variable lengths of time after initiating NSAID treatment. Various antigens and drugs usually acting as haptens causes T-cell activation which starts renal injury (8). Ten to 25% of adult ARF cases are caused by AIN which in fact is a rare epidemiologic factor of pediatric ARF (8). The reason for this difference is not clear yet. A possible explanation might be the fact that majority of NSAID associated ARF cases rapidly resolves and does not necessitate kidney biopsy which leads to underestimation of real incidence. Clinical findings of AIN are highly protean. Increase in urea and creatinine levels is commonly observed besides fever, rash, eosinophilia and eosinophiluria (9). The distinct feature of NSAID associated AIN is that either nephrotic syndrome or renal failure can be the sole manifestastion without accompanying fever, eosinophilia and eosinophiluria. Occasionally, both clinical pictures coexist (3). Our patient did not present with any remarkable clinical finding or eosinophilia/eosinophiluria. However, his renal function rapidly deteriorated with consecutive development of microscopic hematuria and nephritic range proteinuria. Although NSAID associated ARF was reported to be self-resolving in nature (3), more severe cases requiring steroid treatment were also described in current literature (3,4,7). Thus, a renal biopsy was done in order to confirm the diagnosis and predict prognostic outcome.

Acute renal failure cases due to Naproxen induced AIN are very rare in children. Only 5 biopsy proven cases have been reported in current literature to date (3,4,5,7,10) (Table 2). Of these cases, only one patient developed terminal renal failure which was interpreted to be secondary to underlying inflammatory bowel disease. At second month of naproxen treatment, ARF secondary to AIN was observed. Despite naproxen withdrawal and intervention with corticosteroids, the patient developed end stage renal disease (ESRD) after 18 months of follow-up. Repetitive renal biopsies did not demonstrate glomerular involvement attributable to inflammatory bowel disease but chronicity of AIN (7).

Corticosteroid treatment has been recommended in the treatment of severe AIN cases in adults. In terms of pediatric publications of NSAID associated AIN, 2 more cases of corticosteroid usage were reported besides first case described above (3,4). First patient described by Robinson et al. had nephrotic syndrome after naproxen usage and biopsy showed AIN and effacement of podocyte foot processes at glomeruli. The patient responded well to corticosteroid therapy prescibed particularly for nephrotic syndrome (3). The other case was a juvenile rheumatoid arthritis patient who had naproxen associated AIN. Three doses of high dose methylprednisolone were given and therapy was continued with oral prednisolone which resulted in full recovery of patient (4). The remaining cases underwent spontaneous remission like our patient did (5).

In conclusion, we recommend that naproxen sodium should not be prescribed as a first choice drug to treat pediatric pain and inflammation. For professionals taking care of children, it is probably safer to reserve this potentially hazardous and effective medication for rheumatic diseases.

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