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ORIGINAL ARTICLE

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Acute renal failure, associated with non-steroidal anti-inflammatory drugs in healthy children

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Abstract Seven patients aged 13 to 17.5 years developed acute renal failure after treatment with a variety of non-steroidal anti-inflammatory drugs (NSAID): naproxen, diclofenac, ibuprofen, dipyrone and paracetamol. Six of the patients used more than one kind of NSAID. None of the patients had previous history of renal disease or concomitant treatment with other drugs. The time interval between NSAID administration to the emergence of symptoms ranged from 1 to 4 days. The most common presenting symptoms were flank pain (4 patients), abdominal pain (3 patients) and vomiting (3 patients). All patients had normal urine output. Microscopic hematuria and proteinuria were found in 5 patients and leukocyturia in 2. Serum creatinine ranged from 1.3 to 8.3 mg% at presentation. Kidney biopsy was performed in 3 patients and showed findings consistent with mild interstitial inflammation in 1 patient, and normal renal tissue in 2. All patients were treated with intravenous fluids, 1 received corticosteroids. Renal function completely normalized in all patients within 7 to 16 days.

Keywords Interstitial nephritis · Nephrotoxicity · Naproxen · Diclofenac · Dipyrone · Paracetamol

Introduction

Non-steroidal anti-inflammatory drugs (NSAID) are widely used in clinical practice. Acute renal failure (ARF) is a well-known adverse effect of these drugs attributed to inhibition of renal prostaglandin synthesis [1]. It occurs mainly in adult patients in the presence of predisposing risk factors associated with low effective plasma volume. NSAID may also cause ARF by triggering interstitial nephritis [2]. Either form of ARF has been rarely reported after NSAID administration in healthy children and adolescents. We report on 7 previously healthy children, who developed ARF after treatment with NSAID. Six patients used a combination of several NSAID.

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Patients and methods

Seven, previously healthy patients aged 13–17.5 years (4 boys and 3 girls) were admitted to the Schneider Children's Medical Center of Israel during 1998–2003 because of ARF after treatment with different NSAID (naproxen, diclofenac, dipyrone, ibuprofen and paracetamol). Clinical data at presentation is summarized in Table 1. Six patients used more than one medication. Indications for treatment included headache dysmenorrhea and bone fracture. One patient attempted suicide with dipyrone and another with paracetamol. Only for 1 patient were NSAID prescribed by a physician. Presenting symptoms were flank pain (4 patients), abdominal pain (3 patients) and vomiting (3 patients). None of the patients had fever, arthralgia or rash. There was no previous history of renal disease. Three patients (nos 5, 6, and 7) had previously-documented serum creatinine levels which were within a normal range. The patients did not use any medications other than NSAID. Patient 7 was screened for methadione, opiates, cannabinoids, benzodiazepine, cocaine, amphetamine, LSD, and barbiturates but results were negative. Six patients reported vomiting or inadequate (less than usual) fluid intake before or immediately after administration of medications. In 6 patients no signs of dehydration such as weight loss, dryness of skin, tachycardia, hypotension, or delayed capillary filling were observed. One patient (no. 3) had mild dehydration (3.8% weight loss and dry skin).

Urine output and blood pressure were monitored and laboratory studies included urinalysis, 24-hour collection for urinary protein and creatinine, urine sample for sodium and creatinine (before initiation of fluid therapy), complete blood counts, serum creatinine, urea, electrolytes, liver enzymes, albumin, complement (C3 and C4), and anti-nuclear antibodies (ANA). Fractional excretion of sodium was calculated as follows: (urinary sodium×serum creatinine/serum sodium×urinary creatinine)×100%. Renal ultrasonography was performed for all patients. Three patients underwent kidney biopsy.

Table 1 Clinical characteristics

Patient no.	Age (years)	Vomiting/ reduced fluid intake before NSAID	NSAID taken for:	Symptoms after NSAID	NSAID	Duration of therapy (days)	Maximum dose allowed
1	13	Yes	Dysmenorrhea	Abdominal pain, Vomiting, reduced fluid intake	Naproxen 500 mg Diclofenac 150 mg	4	1000 mg day^{-1} 100 mg day^{-1}
2	13	Yes	Dysmenorrhea	Flank pain, Myalgia, Arthralgia, reduced fluid intake	Dipyrone 5000 mg Paracetamol 1500 mg	4	4000 mg day^{-1} 4000 mg day^{-1}
3	17.5	No	Suicidal attempt	Abdominal pain, Vomiting, reduced fluid intake	Paracetamol 4000 mg Ibuprofen 1600 mg	1	4000 mg day^{-1} 2400 mg day^{-1}
4	13	No	Bone fracture	Abdominal pain, Vomiting, reduced fluid intake	Dipyrone 1000 mg Ibuprofen 800 mg	3	4000 mg day^{-1} 2400 mg day^{-1}
5	16	No	Headaches	Flank pain	Ibuprofen 1200 mg Naproxen 500 mg	2	2400 mg day^{-1} 1000 mg day^{-1}
6	17	No	Dysmenorrhea	Fever, Flank pain, Edema, Hypertension	Dipyrone 4000 mg Diclofenac 75 mg Paracetamol 500 mg	4	4000 mg day^{-1} 100 mg day^{-1} 4000 mg day^{-1}
7	16.5	No	Suicidal attempt	Flank pain	Dipyrone 4000 mg	1	4000 mg day^{-1}

Table 2 Clinical data and fluid therapy during first 24 hours from admission

Patient no.	Urine output (mL)	Pulse at admission	Blood pressure at admission	Weight at admission (kg)	Weight at discharge (kg)	Fluid intake IV (mL)	Fluid intake PO (mL)
1	2100	91	119/71	46.4	46.0	1500	1100
2	2800	75	114/70	53.0	49.0	2700	1600
3	1000	80	111/74	63.5	65.0	2400	2200
4	3400	40	120/74	42.0	42.7	2300	250
5	2400	60	115/76	54.0	53.6	1000	2000
6	1700	105	140/83	49.0	47.0	3000	1000
7	3000	81	135/75	69.0	69.0	4000	No data

Results

The time interval between NSAID administration and appearance of the symptoms ranged from 1 to 4 days. Clinical data and fluid therapy during the first 24 hours from admission are summarized in Table 2. None of the patients had significant oliguria or hypotension. One patient had transient hypertension, tachycardia, and peripheral edema. Another patient was mildly dehydrated (weight loss of 3.8%). Results from laboratory investigations are summarized in Table 3. Urine sediment was normal in 2 patients. In four patients microscopic hematuria, leukocyturia, and proteinuria were present. Follow-up urinalysis was normal for all the patients. Urinary protein/creatinine ratio ranged from 0 to 1.22. Fractional excretion of sodium was available for 6 patients and was less than 1% for 2. Serum creatinine and urea at presentation ranged from 1.3–8.3 mg dL^{-1} and 27–110 mg%, respectively. Renal ultrasonography revealed large kidneys with hyperechoic parenchyma for 3 patients and was normal for the remaining patients. Complete blood count, serum levels of sodium, potassium, calcium, and phosphorus, liver enzymes, albumin, complement, and ANA were within normal limits for all patients.

Kidney biopsy was performed for 3 patients and revealed normal renal tissue for 2 patients and mild interstitial inflammation for 1. This patient had no symptoms or signs of allergy (rash, itching or eosinophilia).

All patients were treated with intravenous fluids (NaCl 0.9%) at admission. One patient (no. 7) was treated with corticosteroids (2 mg kg^{-1} day^{-1} prednisone) for a week. Prednisone was tapered down gradually during 4 weeks. Complete recovery of renal function was observed for all patients. The time interval from diagnosis to normalization of renal function ranged from 7–16 days.

Discussion

Seven previously healthy children presented with ARF associated with NSAID use. Duration of treatment was short and the doses, except for one patient, were within the recommended range. NSAID are widely used in adults and children. Acute renal adverse effects of NSAID are well recognized and include vasomotor renal failure at-

Table 3 Results from laboratory investigations

Patient no.	Maximum serum creatinine (mg dL^{-1})	Follow-up serum creatinine (mg dL^{-1})	Time to normalization of renal function (days)	Urinalysis	Urinary protein/ creatinine	Fractional excretion of sodium (%)	Renal ultrasound	Kidney biopsy
1	2.4	0.8	7	Normal	0	Not available	Hyperechoic parenchyma	Not done
2	8.3	0.7	7	WBC 10/ hpf[a] RBC 8/hpf	0	9	Normal	Mild interstitial edema, minimum lymphocytic and eosinophilic infiltrates in the interstitium
3	4.3	1.0	16	RBC 2–5/ hpf	1.22	0.9	Normal	Normal kidney
4	3.1	1.0	10	Normal	0	2.8	Hyperechoic parenchyma	Not done
5	3.6	0.9	15	RBC 5/hpf	0	1.4	Normal	Normal kidney
6	2.4	0.8	14	WBC 3/hpf RBC 4/hpf	0.66	2.6	Normal	Not done
7	1.7	1.1	7	RBC 5/hpf	0.73	0.94	Hyperechoic parenchyma	Not done

[a] high power field

tributed to inhibition of prostaglandin synthesis and interstitial nephritis. Reduced renal perfusion because of reduced effective blood volume causes increased angiotensin activity and leads to renal vasoconstriction. Because renal prostaglandins attenuate the vasonstrictive effect of angiotensin, inhibition of prostaglandin synthesis by NSAID may aggravate renal vasoconstriction.

Many children are treated with NSAID, usually for fever, and when taken as recommended renal failure seems to be uncommon. Assessment of safety of ibuprofen in 84,192 children showed no renal adverse effects [3]. Indeed, acute renal failure rarely develops in the absence of predisposing conditions, associated with reduced effective blood volume or pre-existing renal disease [4]. There are several reports on children who suffered from ARF after treatment with ibuprofen [5, 6]; most of these patients had one of the above mentioned risk factors. Children with acute illness accompanied by fever, vomiting, or diarrhea may suffer from hypovolemia, not necessarily apparent on clinical examination. Most of our patients reported either vomiting or inadequate consumption of fluids before or during treatment with NSAID, although only in one patient was mild dehydration clinically evident at presentation. Thus intravascular volume depletion, even mild, could be one factor contributing to the development of ARF.

A common feature of our patients was simultaneous administration of more than one NSAID. Combination of several NSAID might have aggravated the side effects of each drug. In 1 of our patients ARF occurred after treatment with dipyrone and paracetamol, in another after dipyrone only. Dipyrone is a pyrazolone derivative and paracetamol (known also as acetaminophen) is a *para*-aminophenol derivative. Both medications are analgesic–antipyretics and their effects result from inhibition of prostaglandin synthesis, although to a lesser extent than other NSAID [7]. This may explain why ARF is rare after treatment with recommended doses of paracetamol [8]. Acute renal failure has been reported after paracetamol intoxication and may occur without signs of fulminant liver failure [9]. The molecular mechanisms of paracetamol-induced nephrotoxicity are poorly defined. Animal studies indicate that oxidation of paracetamol by cytochrome P-450 system may result in tubular damage, and that glutathione depletion in the kidney potentiates this process [10]. Paracetamol has been shown to induce apoptosis in murine proximal tubular cells, probably by augmentation of endoplasmatic reticulum stress [11]. It is possible that concomitant use of other NSAID may aggravate the toxicity of paracetamol. NSAID, including dipyrone, have also been associated with interstitial nephritis in adults and children [2, 4, 12].

Seven reports have been published on previously healthy children with transient non-oliguric ARF associated with NSAID [13, 14, 15]. Kidney biopsy was not performed in these cases. All our patients had non-oliguric ARF and complained of abdominal or flank pain. In two patients kidney biopsy revealed the tissue to be normal. Mild interstitial inflammation seen in another patient's biopsy may be attributed to vasomotor changes. Several mechanisms are probably involved in ARF evolution after NSAID treatment. The relative contributions of each of these mechanisms may lead to variations in presenting signs and symptoms. In our patients it is likely that ARF developed as a result of vasomotor changes, some extending to acute tubular necrosis, all non-oliguric, and recovering rapidly with cessation of NSAID therapy and hydration.

Over-the-counter analgesics are usually regarded as safe. Patients use these medications without consulting physicians and may not be aware of potential hazards and predisposing factors aggravating adverse effects. Dehy-

dration is common in children suffering from febrile illnesses and is not always evident. Incidence of renal side effects may actually be higher than estimated, because in most patients they are transient. Although causal relationship between the use of NSAID and ARF can not be determined with confidence in our patients, ARF in 7 previously healthy children with no known risk factors is worrying. Patients should be advised to take NSAID at a recommended dosage, not to use a combination of several NSAID simultaneously, and to consult a physician whenever symptoms such as vomiting or abdominal pain evolve.

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