THREE CASES OF NEPHROTIC SYNDROME TREATED BY INDOMETHACIN

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Abstract

Three cases of nephrotic syndrome treated by indomethacin, either oral capsules or rectal suppositories, are presented. Results showed that indomethacin caused marked reduction in proteinuria and frequency of micturition, loss of oedema fluid and elevation of serum albumin and total protein. These effects were continued after withdrawal of indomethacin in two patients. It could be concluded that indomethacin might have a place in the management of proteinuria, hypoalbuminemia and frequency of micturition. The mode of actions of indomethacin and the role of prostaglandins are discussed (JPMA 38: 54, 1988).

Nephrotic syndrome is usually associated with heavy proteinuria, sodium retention and marked oedema. High doses of corticosteroids, low salt diet and diuretics remain the cornerstone of the management of nephrotic syndrome. The use of immunosuppressive drugs and corticosteroids is not without a risk. However, despite these drugs, the oedema and proteinuria are often poorly controlled and some cases progress to renal failure. Indomethacin and other nonsteroidal antiinflammatory compounds have been shown to play a role in renal physiology, water metabolism, renin release and renal blood flow. They could reduce proteinuria in patients with idiopathic nephrotic syndrome and in a variety of nephridities. In 19 patients with nephrotic syndrome and on low salt diet intake, indomethacin caused immediate decrease in glomerular filtration rate and proteinuria; this effect was completely reversible upon withdrawal of indomethacin therapy. Shehadeh and his associates have found that oral indomethacin therapy resulted in reduction of proteinuria and loss of oedema fluid in a patient with membranous glomerulonephritis and nephrotic syndrome, an effect reversible upon withdrawal of indomethacin. The mode of action of indomethacin remains unclear though a reduction in renal blood flow and glomerular filtration rate have been postulated. This stimulated the use of indomethacin, either oral capsules or rectal suppositories, in three patients with nephrotic syndrome. The mechanism of effects of indomethacin on nephrotic syndrome is discussed.

PATIENTS AND RESULTS

Patient I was a man of 20 years with nephrotic syndrome of five years’ duration. He was treated with corticosteroids, low salt diet and diuretics. He developed hypertension and dyspepsia four years ago which were treated with Hygroton (Chlortidon 50 mg t.d.s.) and antacids. However, during the last year he developed bilateral leg oedema (+ 1), proteinuria (4+) and hypertension despite the treatment. He was admitted several times for investigations and evaluations of his refractory symptoms, but his condition did not show much improvement up to the time of presentation. On examination his blood pressure was 170/100 mmHg, pulse 90 / minute, temperature 36.8 °C, bilateral ankle oedema epigastric tenderness. Investigations revealed a haemoglobin of 12.5 g/dl, normal total and differential white cell count, ESR 58 mm/hr, blood urea 20 mg%, serum creatinine 0.8 mg%, serum uric acid 6.7mg% serum cholesterol 370 mg%, serum albumin 2.2 % and total protein 4 mg %. Urinalysis
showed albuminuria (4+), and 24—hour urinary protein excretion was 5.7 gram. Rheumatoid factor and anti-DNA antibodies were negative. Intravenous urogram showed normal functioning kidneys. Renal biopsy revealed membranous proliferative glomerulonephritis. A decision was made to begin an open trial of indomethacin rectal suppositories. After an informed consent 100 mg of indomethacin rectal suppository was prescribed twice daily. Twenty four hour urinary protein decreased to 1.3 gram, blood pressure had dropped to 130/80 mm Hg, and frequency of micturition and ankle oedema disappeared after three weeks therapy. Serum albumin and total serum protein increased to 3.4 g % and 5.9 g % respectively. Then the dose of indomethacin was reduced to 100 mg per day. Renal function tests remained normal and urinary protein excretion less than 1.4 gram until the treatment was discontinued at 12 weeks. Two weeks later, urinary protein excretion had risen to 3.7 gram. Therefore, indomethacin therapy was reinstituted (one suppository/day) and two weeks later, urinary protein excretion decreased to 1.6 gram. The patient continues to receive indomethacin suppository (100 mg every other day) without side effects, and urinary protein excretion remains less than 1.3 gram. Blood urea, serum creatinine, serum cholesterol, serum uric acid and serum electrolytes remain within normal limits. Patient 2 was a man of 45 years. He presented with general weakness, dyspepsia, frequency of micturition (more than 17 times/day) and oedema of three weeks’ duration. Past history was unremarkable. On physical examination, the blood pressure was 130/90 mmHg, pulse 85/minute and the temperature was 37.1 °C. There was pitting pretibial oedema (3+). Laboratory investigations showed a haemoglobin 12 g/dl, white cell count 6000cell/Cmm with a normal differential count, ESR 45 mm/hr, blood urea 35 mg %, serum creatinine 1 mg%, serum uric acid 6.5 mg %, serum albumin 2.1 mg%, serum cholesterol 400 mg% and total serum protein 4.3 g%. Liver function tests were normal. Intravenous urogram showed normal functioning kidneys. Urinalysis revealed albuminuria (3+), granular cast(+) and few red and white blood cells. Twenty four hour urinary protein excretion was 5.5 gram. Rheumatoid factor and anti—DNA antibodies were negative. ASOT was 150 I.U/l. Renal biopsy was not performed. After informed consent, the patient was treated with 100 mg of indomethacin suppositories given twice daily. The frequency of micturition reduced (less than six/day), urinalysis showed no albuminuria after two weeks and leg oedema disappeared after three weeks. Twenty four hour urinary protein excretion had decreased to 0.3 gram and serum albumin had risen to 3.3 g% at four weeks. Laboratory investigations remained normal and the treatment was discontinued after six weeks. Six months follow-up was uneventful. Patient 3 was a woman of 20. She presented with frequency of micturition (more than 20/day) generalized oedema, backache and loss of appetite of two weeks’ duration. Her general health was excellent. This was the first urinary symptoms. On physical examination, her blood pressure was 110/70 mmHg, the pulse 88/ minute and temperature was 37.2 °C. There was pitting oedema of legs, hand and sacrum. Her haemoglobin was 14 g/dl, white cell count 7100 /Cmm, normal differential count, ESR 55 mm/hr, blood urea 30 mg %, serum creatinine 0.6 mg %, fasting blood sugar 80 mg % and ASOT 140 I.U/l. Anti—DNA antibodies and Rheumatoid factor were negative. Liver function tests, serum electrolytes, chest x-ray and intravenous urogram were also normal. Serum protein was 3.5 g% and serum albumin was 1.4 g%. Urinalysis showed albuminuria (4+) granular cast (1+) and few pus cells and red blood cells. Twenty four hour urinary protein excretion was 43 gram. Renal biopsy was not performed. The patient was treated with low salt diet, Furosemide (20 mg t.d.s.) and indomethacin capsule (25 mg t.d.s.). The oedema gradually subsided and disappeared after two weeks. The diuretic was then withdrawn with liberalization of normal salt intake. Urinalysis showed albuminuria (1+) and no cast, a 24—hour urinary protein excretion was 1.4 gram after four weeks. The frequency of micturition was reduced to less than five times per day. Twenty four hour urinary protein excretion was 0.2 gram, serum albumin was 3.2 g% and serum total protein was 6.1 g% after eight weeks therapy. Laboratory investigations remained within normal limits. Then, indomethacin therapy was withdrawn at ten weeks and the patient was well on six months follow-up.
DISCUSSION

Indomethacin therapy was found to be useful in the management of proteinuria in patients with nephrotic syndrome, with attendant symptomatic relief. One patient had steroid resistant nephrotic syndrome and hypertension. He was treated with indomethacin suppositories four years after the diagnosis of the disease. This treatment resulted in a significant reduction of proteinuria, loss of oedema and elevation of both serum albumin and total serum protein. These effects were reversed upon withdrawal of indomethacin therapy. The other two patients were treated with indomethacin immediately after the diagnosis. One patient was treated with diuretics, low salt diet and indomethacin capsules. This caused marked improvement that allowed both liberalization of salt intake and withdrawal of diuretics, an improvement which continued after withdrawal of indomethacin. The other patient was treated with indomethacin suppositories which resulted in prompt and sustained improvement. Early institution of indomethacin therapy in acute stage of the disease might be responsible for the sustained improvement obtained in two patients. On the other hand, this might be the result of spontaneous remission. However, further investigations are necessary to explain the sustained improvement. One patient was treated with oral indomethacin while the other two patients were treated with indomethacin rectal suppositories. These two patients had indigestion and epigastric pain so it was thought that oral indomethacin might worsen such symptoms. No side effects including nausea, vomiting, headache, dizziness, vertigo and skin rash were noticed with use of indomethacin either oral capsules or rectal suppositories. The therapeutic effects of indomethacin in patients with nephrotic syndrome might be the result of inhibition of prostaglandin biosynthesis though there has been no attempt to measure urinary prostaglandin. It has been shown that prostaglandins could affect salt and water metabolism, renal blood flow, renin release and renal vascular resistance\(^7\). Moreover, in our earlier observation\(^8\), prostaglandin caused significant reduction in serum albumin and changes in total serum protein during prolonged antigenic stimulation. It was postulated that this reduction might be the result of increased albumin leakage through glomerular membrane or/and decreased albumin synthesis in the liver. However, this could explain the elevation of serum albumin and serum total protein observed in patients with nephrotic syndrome when prostaglandin biosynthesis was inhibited with use of indomethacin. The exact pathology of renal lesions was not known in two of the patients since renal biopsy was not performed. Due to shorter duration of illness it was decided to treat these two patients in acute stage of the disease where it was inadvisable to perform renal biopsy before institution of the therapy. Nevertheless, indomethacin therapy resulted in marked reduction of proteinuria and frequency of micturition, elevation of albumin and total serum protein and loss of oedema. These effects were also observed in the patient with resistant nephrotic syndrome. It has been reported that prostaglandin synthesis inhibitors, including indomethacin, caused moderate and reversible deterioration in renal functions when they were used in patients with renal lesions\(^2\). However, these were unusual observations since indomethacin has been shown to reduce proteinuria in patients with idiopathic nephrotic syndrome, and long-term use of nonsteroidal anti-inflammatory compounds has never been shown to cause chronic renal failure in human beings\(^2-5\). This clinical trial is an open study and is of limited value. Therefore, further investigations and controlled studies should be conducted to evaluate the beneficial effects of indomethacin in patients with proteinuria, hypoalbuminemia and frequency of micturition.

REFERENCES