# THE EFFECT OF PIRPROFEN ON RENAL FUNCTION IN MAN

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## SYNOPSIS

**The possible renal side effects of pirprofen were studied for a short period, after administration of the drug. As indexes for estimating the renal function, 24th urine output, urianalysis, qualitative proteinuria analysis, glomerular filtration rate determination, blood urea, serum creatinine, serum Na and K were used. No statistically significant changes of the values of the above parameters were observed after administration of the drug. Our results indicate that pirprofen is a safe anti-inflammatory drug for the renal function, at least when administered for a short period.**

## INTRODUCTION

Pirprofen is a new nonsteroidal anti-inflammatory agent for the treatment of various rheumatic conditions. It is known that NSAIDs are potent inhibitors of prostaglandin synthesis not only at the site of inflammation but in most, if not all organs in the body. Since prostaglandins are important regulators of renal haemodynamics, the inhibition of their synthesis in the kidney induced by NSAIDs would explain the subsequent changes in renal function (1,2,3). As pirprofen is a relatively potent inhibitor of prostaglandin synthetase is seemed to us reasonable to study the effect of this drug on renal function in man.

## MATERIAL AND METHODS

Fifteen volunteers, 9 males and 6 females aged 18—79 (mean 48) comprised the group of this study (Table I). Ten out of them were healthy adults (N), 3

**TABLE I: CHARACTERISTICS OF THE MATERIAL STUDIED**

| No | Initials | Sex | Age | Condition |
|---|---|---|---|---|
| 1 | MG | F | 32 | SLE |
| 2 | SM | M | 56 | N |
| 3 | HT | M | 79 | N |
| 4 | SS | F | 67 | N |
| 5 | MG | F | 46 | MCTD |
| 6 | DP | F | 46 | N |
| 7 | KC | M | 35 | N |
| 8 | CM | M | 18 | N |
| 9 | KP | F | 73 | N |
| 10 | DT | M | 50 | N |
| 11 | BE | M | 49 | RA |
| 12 | DB | F | 60 | RA |
| 13 | FA | M | 25 | RA |
| 14 | LS | M | 31 | N |
| 15 | IK | M | 52 | N |

SLE: Systemic Lupus Erythematosus
N: Normal
MCTD: Mixed Connective Tissue Disease
RA: Rheumatoid Arthritis

were suffering from active rheumatoid arthritis, 1 from non active systemic lupus erythematosus and 1 from active mixed connective tissue disease. Four hundred mg of pirprofen were given to each volunteer 3 times daily for a period of 7 days.

The complete investigation for each one of them included 24th urine output, urianalysis, qualitative proteinuria analysis, glomerular filtration rate determination (GFR), blood urea, serum creatinine, serum sodium and potassium. The whole investigation was performed before administration of the drug, and after 3 and 8 days.

Qualitative proteinuria analysis has been carried out by means of DISK sodium Dodecyl sulfate Polyaccrylamide gel electrophoresis (Disk-SDS-PAGE) according to Laemmli (4).

For the GFR determination we used Cr-51 EDTA. Blood urea and serum creatinine were measured by conventional methods and serum sodium and potassium using absorption spectrophotometer.

## RESULTS

The results from this study are summarized in Table II and III. Table II shows the GFR calculated values of

**TABLE II: GFR VALUES OBTAINED DURING OUR INVESTIGATION (ML/MIN/1.73 M²)**

| | Before | After | |
|---|---|---|---|
| No | | 3 days | 8 days |
| 1 | 95 | 93 | 93 |
| 2 | 103 | 76 | 78 |
| 3 | 110 | 106 | 90 |
| 4 | 96 | 80 | 78 |
| 5 | 80 | 88 | 89 |
| 6 | 120 | 123 | 135 |
| 7 | 158 | 136 | 138 |
| 8 | 134 | 121 | 115 |
| 9 | 104 | 104 | 106 |
| 10 | 151 | 148 | 134 |
| 11 | 101 | 96 | 93 |
| 12 | 97 | 97 | 91 |
| 13 | 115 | 112 | 102 |
| 14 | 112 | 114 | 120 |
| 15 | 98 | 99 | 105 |

**TABLE III: LABORATORY DATA OF THE MATERIAL STUDIED**

| | Urea (gm/l) | | | Creatinine (mg/dl) | | | Na (mEq/1) | | | K (mEq/1) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No | Before | After | | Before | After | | Before | After | | Before | After | |
| | | 3 days | 8 days | | 3 days | 8 days | | 3 days | 8 days | | 3 days | 8 days |
| 1 | 0.50 | 0.55 | 0.48 | 0.98 | 1.03 | 0.90 | 145 | 150 | 146 | 4.5 | 5.0 | 4.6 |
| 2 | 0.30 | 0.41 | 0.32 | 1.42 | 1.28 | 1.30 | 140 | 144 | 150 | 4.8 | 4.6 | 5.1 |
| 3 | 0.34 | 0.40 | 0.49 | 0.50 | 0.60 | 0.50 | 144 | 140 | 148 | 4.7 | 4.5 | 5.0 |
| 4 | 0.57 | 0.60 | 0.58 | 1.25 | 1.42 | 1.30 | 155 | 152 | 148 | 5.2 | 5.0 | 4.9 |
| 5 | 0.30 | 0.35 | 0.30 | 0.39 | 0.50 | 0.86 | 148 | 146 | 148 | 4.8 | 4.6 | 4.8 |
| 6 | 0.46 | 0.44 | 0.51 | 0.50 | 0.60 | 0.50 | 146 | 145 | 148 | 4.8 | 4.6 | 4.8 |
| 7 | 0.35 | — | 0.44 | 1.00 | — | 1.1 | 140 | — | 145 | 4.8 | — | 4.8 |
| 8 | 0.52 | 0.54 | 0.50 | 1.00 | 1.2 | 0.9 | 148 | 150 | 148 | 4.8 | 5.0 | 5.1 |
| 9 | 0.30 | 0.30 | 0.32 | 0.5 | 0.61 | 0.6 | 137 | 140 | 140 | 3.8 | 5.0 | 5.0 |
| 10 | 0.33 | 0.30 | 0.35 | 10 8 | 1.0 | 1.1 | 148 | 150 | 148 | 4.6 | 4.8 | 4.6 |
| 11 | 0.33 | 0.38 | 0.38 | 0.9 | 0.9 | 0.8 | 149 | 151 | 149 | 3.9 | 4.1 | 4.1 |
| 12 | 0.32 | 0.31 | 0.31 | 0.51 | 0.52 | 0.51 | 138 | 141 | 141 | 4.7 | 4.5 | 4.7 |
| 13 | 0.30 | 0.30 | 0.31 | 1.23 | 1.29 | 1.28 | 144 | 143 | 146 | 4.8 | 4.6 | 4.6 |
| 14 | 0.34 | 0.34 | 0.32 | 0.51 | 0.51 | 0.50 | 147 | 149 | 147 | 4.8 | 4.5 | 5.0 |
| 15 | 0.40 | 0.40 | 0.41 | 0.50 | 0.50 | 0.43 | 147 | 146 | 149 | 4.3 | 4.8 | 4.4 |

each person before administration of the drug, also 3 and 8 days after it. Table III shows the obtained values for blood urea, serum creatinine, serum Na and K. Table IV shows the significance of the differences between the mean values of the parameters studied. In none of our cases anuria or oligouria developed and the changes of the 24th urine output were less than 150 cc. No abnormalities were observed in the urinanalysis. In the qualitative analysis, only in 2 of our cases low molecular weight, 15000 and 50000 respectively, proteins were detected but in very low quantities in the DISK-SDS-PAGE. In the glomerular filtration rate determination a GFR reduction greater than 14% (18%, 19% and 26%) has been observed only in 3 healthy adults out of 10, but no significant difference was present between the GFR values when all persons studied were considered as a group (Table IV). Not one of our patients presented a GFR reduction greater than 11%. No significant difference was observed between values of blood urea, serum creatinine, serum Na an K when compared before and after administration of the drug.

dysfunction. However, this remains an open question, especially for evaluating the safety of the drug after longer periods of administration. A GFR reduction greater than 14% has been observed only in 3 healthy adults, as stated before, but it has to be mentioned that our No 2 case with the 26% GFR reduction was nephrectomized many years ago due to pyonephrosis. As no significant difference is observed between the GFR values when all persons studied were considered as a group, no abnormality could be considered to occur on the renal function, concerning the GFR rate after administration of the studied agent. Concerning our patient, although alterations of renal function after administration of NSAIDs have been reported mainly in rheumatic patients, not one of our studied patients showed a GFR reduction greater than 11%. Comparing the biochemical parameters studied (blood urea, serum creatinine, serum Na and K) before and after administration of the drug, no significant difference was observed between them.

Hyperkalemia has been described during treatment with indomethacin in patients with chronic renal

**TABLE IV: SIGNIFICANCE OF THE DIFFERENCES BETWEEN MEAN VALUES OF THE PARAMETERS STUDIED**

| | Before — 3 days after | Before — 8 days after | 3 days after — 8 days after |
|---|---|---|---|
| GFR | $t = 2.13$ | $t = 2.14$ | $t = 1.1$ |
| | $p \sim 0.1$ | $0.1 > p > 0.05$ | $p > 0.1$ |
| Blood | $t = 2.15$ | $t = 0.30$ | $t = 0.31$ |
| Urea | $0.1 > p > 0.05$ | $p > 0.1$ | $p > 0.1$ |
| Serum | $t = 2.1$ | $t = 0.83$ | $t = 0.75$ |
| Creatinine | $0.1 > p > 0.05$ | $p > 0.1$ | $p > 0.1$ |
| Na | $t = 0.66$ | $t = 0.24$ | $t = 0.21$ |
| | $p > 0.1$ | $p > 0.1$ | $p > 0.1$ |
| K | $t = 0.71$ | $t = 1.55$ | $t = 1$ |
| | $p > 0.1$ | $p > 0.1$ | $p > 0.1$ |

## DISCUSSION

Administration of NSAIDs, known inhibitors of the prostaglandin synthesis, has been established to produce several alterations in renal function. Glomerulonephritis, interstitial nephritis and papillary necrosis have been reported in rats after administration of fenoprofen, naproxen and tolmetin as referred in the manufacturer's literature. Galler et al (5) observed within a very short time 5 cases of reversible acute renal failure in patients with preexisting mild insufficiency receiving indomethacin. Gary et al (6) reported a case in which acute renal failure followed indomethacin therapy in a patient who had no prior renal impairment. Reversible renal failure, nephrotic syndrome and interstitial nephritis have been reported in patients receiving fenoprofen, naproxen and tolmetin (7,8).

The present study was designed to evaluate the possible renal side effects of pirprofen in man. In the qualitative analysis, low molecular weight, 15000 and 50000 respectively, proteins were detected only in 2 of our cases but in very low quantities in the DISK-SDS-PAGE. Detection of 2 low molecular weight fractions in DISK-SDS-PAGE does not mean by anyway a tubular failure (9,19,11) and in patients with multiple myeloma (12). In conclusion, compelling evidence is accumulated from our study that pirprofen is a safe anti-inflammatory agent for the renal function at least when given for a short period, but as with all other anti-inflammatory agents, it has to be administered with special care in people with preexisting renal impairment. Possible side effects of the drug after prolonged use is an open question to research.

## REFERENCES


1. Kimberly RP, Bowden RE, Keiser HR, Plotz PH: Reduction of renal function by newer nonsteroidal anti-inflammatory drugs. Am J Med 1978; 64: 804-7.
2. Walshe JJ, Venuto RC: Acute oliguric renal failure induced by Indomethacin: Possible mechanism. Ann Intern Med 1979; 91: 47-9.
3. Dunn MJ, Zambraski EJ: Renal effects of drugs that inhibit prostaglandin synthesis. Kidney Int 1980; 18: 609-22.
4. Laemmli UK: Cleavage of structural-proteins during the assembly of the head of bacteriophage T4. Nature 1970; 227: 680-5.

5. Gallen M, Folkert VW, Schlondorff D: Reversible acute renal insufficiency and hyperkalemia following indomethacin therapy. JAMA 1981; 246: 154-5.
6. Gary NE, Dodelson R, Eisinger RP: Indomethacin-associated acute renal failure. Am J Med 1980; 69: 135-6.
7. Brezin JH, Katz SM, Schwartz AB, Chinitz JL: Reversible renal failure and nephrotic syndrome associated with nonsteroidal anti-inflammatory drugs. N Engl J Med 1979; 301: 1271-3.
8. Katz SM, Capaldo R, Everts EA, DiGregorio JG: Tolmetin association with reversible renal failure and acute interstitial nephritis. JAMA 1981; 246: 243-5.
9. Kutyrina IM, Androsova SO, Tareyeva IE: Indomethacin-induced hyporeninemic hypoaldosteronism. Lancet 1979; i: 785.
10. Tan SY, Burton M: Hyporeninemic hypoaldosteronism. An overlooked cause of hyperkalemia. Arch Intern Med 1981; 141: 30-3.
11. Tan SY, Shapiro R, Franco R, Stockard H, Mulrow PJ: Indomethacin-induced prostaglandin inhibition with hyperkalemia. Ann Intern Med 1979; 90: 783-5.
2. Papadini G, Tonazzi C: Indomethacin-induced hyperkalemia and renal failure in multiple myeloma. Acta Haematol 1982; 68: 256-60.