Journal of Biological Research **7**: 105 – 108, 2007
J. Biol. Res. is available online at http://www.jbr.gr
Indexed in: CAS (Chemical Abstracts Service) and DOAJ (Directory of Open Access Journals)

— SHORT COMMUNICATION —

Comparative studies of paracetamol and ibuprofen alone and in combination on renal function of guinea pigs

HARRISON U. NWANJO* and GABRIEL O. OZE

College of Medicine and Health Science, *Imo State University*, *Owerri*, *Nigeria*

Received: 8 February 2007 Accepted after revision: 4 April 2007

Paracetamol and ibuprofen alone and in combination on renal function of guinea pigs were evaluated in this study. We assessed renal parameters such as urea, creatinine, and electrolyte. The guinea pigs were divided into four groups of six. Group I received only food and water (control). Groups II-IV received in addition to food and water either a single dose of paracetamol (15 mg kg^{-1} day^{-1}) and ibuprofen (10 mg kg^{-1} day^{-1}) or a combined therapy of paracetamol and ibuprofen for 14 days. The ibuprofen treated group showed a significant increase in serum urea and creatinine ($p < 0.05$) and a decrease in serum sodium ion levels ($p < 0.05$), when compared with the corresponding values of the control group. Administration of paracetamol showed no significant difference in all the parameters assessed when compared with the control group. This study showed that combined administration of paracetamol and ibuprofen caused a pronounced increase in serum urea, creatinine and a decrease in serum sodium levels. These results suggest that ibuprofen affects kidney function, more so when administered with paracetamol. This combination of drugs is commonly used in reducing fever and pains associated with malaria, and rheumatoid arthritis in tropical countries such as Nigeria.

Key words: paracetamol, ibuprofen, renal function.

INTRODUCTION

Paracetamol is one of the most commonly used non-steroidal anti-inflammatory drugs (NSAIDs) (Hardman *et al*., 2001). It is a rapid, reversible, non-competitive inhibitor of the cyclo-oxygenase activities and thus the arachidonic acid cascade. It is believed to be a weak inhibitor of prostaglandin synthesis.

Renal prostaglandins (PGs) are vasodilators that play important roles in the preservation of kidney function when activities of the rennin-angiotensin system or the renal sympathetic nerves are elevated. They act to maintain glomerular filtration rate (GFR) and renal blood flow (RBF) by modulating the effects of vasoconstrictors such as ANG II or norepinephrine on the renal vascular smooth muscles (Dunn & Zambraski, 1980). Since paracetamol is a weak inhibition of PG synthesis, it is predicted to have no deleterious effect on the kidney in a renal PG-dependant state.

There are, however, isolated medical case reports on renal vasoconstriction and acute renal failure resulting from therapeutic paracetamol use (Bonkovsky *et al*., 1994; Blakely & McDonald, 1995; Ojiako & Nwanjo, 2006). There is also a report suggesting that paracetamol may induce renal failure arising from renal insufficiency (Berg *et al*., 1990).

Ibuprofen and other non-steroidal anti-inflammatory drugs such as aspirin and indomethacin, have been shown to significantly reduce prostaglandin E_2 (PGE_2) synthesis and consequently adversely alter kidney function in humans (Laffi *et al*., 1986; Bippi & Frolich, 1990) and animals (Zambraski *et al*., 1988).

Paracetamol in combination with ibuprofen ("I-bumol") are commonly used in reducing fever and pains associated with malaria and rheumatoid arthritis in tropical countries such as Nigeria. Such self-

* Corresponding author: tel.: +23 408033525389, e-mail: harrisonnwanjo@yahoo.co.uk

medication is very common in some developing countries like Nigeria, and sometimes at doses above the therapeutic ones. It is therefore the aim of this study to evaluate the renal action of separately administered oral paracetamol or ibuprofen and compare these with combined administration of the drugs.

MATERIALS AND METHODS

Animals

Twenty-four guinea pigs were purchased from the Animals Science Unit of the Michael Okpara University of Agriculture, Umudike, Nigeria and were held at the Animal House of College of Medicine and Health Sciences, Imo State University, Owerri. They had free access to food (commercial chow, products of Guinea Feeds Ltd, Benin, Nigeria) and water. The animals were acclimatized at laboratory conditions for one week. The weight of the animals prior to the study ranged between 300 and 500 g.

Drugs

Paracetamol (acetaminophen) tablets used in the experiment were manufactured by Emzor Pharmaceutical Industries Ltd, Lagos, Nigeria and ibuprofen (brustan-N) tablets were the product of Ranbaxy Laboratories Ltd, Dewas, India.

Experimental design

Animals were randomly assigned to four experimental groups of six guinea pigs each. Group I animals (control group) received only food and water with no drugs.

The other groups received food and water and in addition, group II received paracetamol (15 mg kg^{-1} day^{-1}), group III ibuprofen (10 mg kg^{-1} day^{-1}), and group IV paracetamol along with ibuprofen. The drugs were administered to the animals by oral compulsion for 14 days and the renal parameters were studied.

Blood sample collection

Twenty four hours after the last doses were administered the animals were anaesthetized with chloroform vapour, quickly brought out of the jar and sacrificed. Whole blood was collected by cardiac puncture from each animal into clean, dry centrifuge tubes. The blood was allowed to stand for about 30 min to clot and further centrifuged at 10,000 rpm for 5 min using a Wisperfuge model 1384 centrifuge (Samson, Holland). Serum was separated from the clot with a Pasteur pipette into sterile serum sample tubes and used for biochemical assays.

Biochemical assays

Urea concentration was measured using the diacetyl monoxine method of Marshal (1957), while creatinine concentration was determined with the alkaline picrate method (Tietz *et al*., 1986). Serum sodium and potassium concentrations were determined using a reagent set (Tietz *et al*., 1986). Serum bicarbonate concentration was determined titrimetrically. Serum chloride concentration was determined using the mercuric nitrate method (Schales & Schales, 1941).

Statistical analysis

Statistical evaluation of data was performed by using one way analysis of variance (ANOVA), followed by Duncan's multiple range test (Duncan, 1957).

RESULTS

The changes in the mean values of serum urea and creatinine concentrations in both control and experimental animals are shown in Table 1. The mean values of urea and creatinine in the serum showed no significant difference ($p > 0.05$) in the animals treated with ibuprofen alone, however they showed a significant increase ($p < 0.05$) in both urea and creatinine levels, when compared with the control group. The group of animals treated with a combined therapy of paracetamol and ibuprofen showed a significant

TABLE 1. Mean values (± SD) of serum urea and creatinine in both control and experimental groups

	Control (group I)	Group II	Group III	Group IV
Urea (mg dl^{-1})	9.82 ± 0.38	10.64 ± 0.58	14.92 ± 0.55*	18.32 ± 1.27**
Creatinine (mg dl^{-1})	0.82 ± 1.08	0.98 ± 1.06	1.38 ± 1.16*	2.07 ± 1.29**

* = significantly different from control ($p < 0.05$)
** = significantly different from control and group III ($p < 0.05$)

TABLE 2. Mean values (± SD) of serum electrolytes in both control and treated groups

	Control (group I)	Group II	Group III	Group IV
Sodium(mmol l^{-1})	142.70 ± 0.74	142.91 ± 1.85	148.42 ± 1.08*	162.44 ± 2.84**
Potassium (mmol l^{-1})	2.85 ± 0.31	3.06 ± 0.40	3.18 ± 0.40	3.08 ± 0.35
Bicarbonate (mmol l^{-1})	25.85 ± 0.55	24.95 ± 0.51	24.75 ± 0.49	24.98 ± 1.81
Chloride (mmol l^{-1})	113.96 ± 1.94	114.16 ± 0.56	113.90 ± 0.60	113.76 ± 1.62

* = significantly different from control ($p < 0.05$)
** = significantly different from control and group III ($p < 0.05$)

increase ($p < 0.05$) in the mean serum urea and creatinine levels when compared with the control and the single therapy groups.

Table 2 shows the mean values of serum electrolyte concentration in both the test and control groups. The ibuprofen treated animals showed a significant decrease ($p < 0.05$) in sodium and potassium levels when compared with the control group. The animals treated with a combined therapy of paracetamol and ibuprofen showed significant decreases ($p < 0.05$) in the mean serum sodium level when compared with the control or the single therapy groups. There was no significant difference ($p > 0.05$) in the mean values of bicarbonate and chloride levels across groups.

DISCUSSION

The results of this study revealed that separately administrated ibuprofen increased the serum urea and creatinine and decreased the serum sodium ions (hyponatraemic effect), which showed that acetaminophen and ibuprofen alter the renal function. Ibuprofen and other NSAIDs, such as piroxicam and indomethacin have been shown to significantly reduce PGE_2 synthesis and consequently adversely alter kidney function in both humans (Bippi & Frolich, 1990) and animals (Zambraski *et al*., 1988). The possible cause of these effects may be linked with the fact that the drug inhibits the synthesis of prostaglandins by blocking the cyclo-oxygenase which is responsible for the conversion of arachidonic acid to prostaglandins. Although prostaglandins are not the key renal blood flow mediators in healthy individuals, the inhibition of their synthesis tends to reduce the renal blood flow with a consequent fall of the GFR and hence an increase of the serum urea and creatinine (Marcia, 2000). Prostaglandins have also been shown to increase sodium excretion and inhibit active transport of NaCl in the thick ascending limbs and cortical collecting duct of isolated profused nephrons (Villa *et al*., 1997). Hence, inhibition of prostaglandins will cause an increase of the serum sodium and chloride concentrations. The group of animals administrated with paracetamol had no significant change of the serum urea, creatinine and electrolytes when compared with the control. Thus, paracetamol, in contrast to ibuprofen, would not be assumed to have a deleterious effect on the kidney. Paracetamol has been found to have an effect on GFR in normal subjects (Bippi & Frolich, 1990). It is the recommended therapy for subjects with renal dysfunction (Insel, 1996) although there are isolated medical case reports on renal vasoconstriction and acute renal failure resulting from therapeutic paracetamol use (Bonkovsky *et al*., 1994; Blakely & McDonald, 1995). The effects of paracetamol were far less than those seen with ibuprofen. These data suggest that paracetamol has less potential to adversely affect renal function under normal renal conditions.

We also showed that the combined administration of ibuprofen, which is often used as an antipyretic and anti-inflammatory agent, caused a marked increase in serum urea, creatinine, Na^+ and K^+ in guinea pigs. This could be explained since ibuprofen ingestion impairs urinary concentrating ability in animals (Burrell *et al*., 1990). Paracetamol administration against a background of analgesic nephropathy might be expected to cause a pronounced adverse effect which may be of clinical significance in patients suffering from dehydration and electrolyte imbalance (Kaysen *et al*., 1985).

It is therefore concluded that ibuprofen affects kidney function, more so when administered with paracetamol. These results suggest that a closer monitoring is needed in patients under combined therapy of paracetamol and ibuprofen because of its effect on renal function in humans since the combination of these drugs is commonly used in managing fever and pains associated with malaria and rheumatoid arthri-

tis in tropical countries such as Nigeria. The combination of paracetamol and ibuprofen should be administered with caution or avoided in patients predisposed to stress, hypertension, cardiac and hepatic dysfunctions and renal insufficiency.

REFERENCES

Berg KJ, Djoseland O, Gjellan A, Hundal O, Khudseh ER, Rugstad HE, Rinneberg E, 1990. Acute effects of paracetamol on prostaglandin synthesis and renal failure in normal man and in patients with renal failure. *Clinical nephrology*, 3: 255-262.

Bippi H, Frolich JC, 1990. Effects of acetylsalicylic-acid and paracetamol alone and in combination on prostanoid synthesis in man. *British journal of clinical pharmacology*, 29: 305-310.

Blakely P, McDonald BR, 1995. Acute renal failure due to acetaminophen ingestion: a case report and review of the literature. *Journal of the american society of nephrology*, 6: 48-53.

Bonkovsky HL, Kane RE, Jones DP, Galinsky RE, Banner B, 1994. Acute hepatic and renal toxicity from low doses of acetaminophen in the absence of alcohol abuse or malnutrition: evidence for increased susceptibility to drug toxicity due to cardiopulmonary and renal insufficiency. *Hepatology*, 19: 1141-1148.

Burrell JH, Yong JL, MacDonald GJ, 1990. Experimental analgesic nephropathy: Changes in renal structure and urinary concentrating ability in Fischer 344 rats given continuous low doses of aspirin and paracetamol. *Pathology*, 22: 33-44.

Duncan BD, 1957. Multiple range test for correlated and heteroscedastic means. *Biometrics*, 13: 359-364.

Dunn MJ, Zambraski EJ, 1980. Renal effects of drugs that inhibit prostaglandin synthesis. *Kidney international*, 18: 608-622.

Hardman JG, Limbird LE, Gilman AG, 2001. *Goodman and Gilman's – The pharmacological basis of therapeutics*. McGraw & Hill, New York.

Insel PA, 1996. Analgesic-antipyretic and antiinflammatory agents and drugs employed in the treatment of gout. In: Hardman JG, Limbird LE, Gilman AG, eds. *Goodman and Gilman's – The pharmacological basis of therapeutics*, 9th edition. McGraw & Hill, New York: 617-658.

Kaysen GA, Pond SM, Roper MH, Menke DJ, Marrama MA, 1985. Combined hepatic and renal injury in alcoholics during therapeutic use of acetaminophen. *Archives of internal medicine*, 145: 2019-2023.

Laffi G, Daskalopoulos G, Kronborg I, Hsueh W, Gentilini P, Zipser RD, 1986. Effects of sulindac and ibuprofen in patients with cirrhosis and ascites. An explanation for the renal-sparing effect of sulindac. *Gastroenterology*, 90: 182-187.

Marcia LB, 2000. Ibuprofen-associated renal toxicity in children. *Pediatric pharmacotheraphy*, 6: 111-116.

Marshal WH, 1957. Urea estimation by thiosemicarbazide method. *American journal of clinical pathology*, 28: 681-682.

Ojiako OA, Nwanjo HU, 2006. Effects of co-administration of chloroquine with paracetamol or ibuprofen on renal function of rabbits. *African journal of biotechnology*, 5: 668-670.

Schales O, Schales SS, 1941. A simple and accurate method for the determination of chloride in biological fluids. *Journal of biological chemistry*, 140: 879-884.

Tietz NW, Pruden EL, Siggard-Anderson O, 1986. Electrolytes, blood gases and acid-base balance. In: Tietz NW, ed. *Textbook of clinical chemistry*. Saunders, Philadelphia: 1179-1180.

Villa E, Garcia-Robles R, Haas J, Romero JC, 1997. Comparative effect of PGE_2 and PGI_2 on renal function. *Hypertension*, 30: 664-666.

Zambraski EJ, Atkinson DC, Diamond J, 1988. Effects of salicylate vs. aspirin on renal prostaglandins and function in normal and sodium depleted dogs. *Journal of pharmacology and experimental therapeutics*, 247: 96-103.