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Short Communication

Effects of co-administration of chloroquine with paracetamol or ibuprofen on renal function of rabbits

Okey A. OJIAKO[1]* and Harrison U. NWANJO[2]

[1]Department of Biochemistry, Federal University of Technology, Owerri, Nigeria.
[2]Department of Medical Laboratory Sciences, Imo State University, Owerri, Nigeria.

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The effects of co-administration of oral chloroquine with paracetamol or with ibuprofen on renal function were studied using 6 groups of New Zealand White rabbits. Group 1, the control group received only feed and water. The other groups (Groups 2-6) either received single therapies of paracetamol (10 mg/kg of body weight every 6 hours), ibuprofen (20 mg/kg of body weight/day) or chloroquine (5 mg/kg of body weight/day) or combined therapies of chloroquine and paracetamol or chloroquine and ibuprofen for 8 days. Measurements of serum urea, creatinine and electrolyte concentrations were used to assess renal function in these animals. The chloroquine-treated group had a significant ($p<0.05$) decrease in serum sodium and potassium concentrations and a significant increase ($p<0.05$) in serum urea and creatinine concentrations when compared with the corresponding values of the control group. The groups treated with combined therapy (groups 5 and 6) had significant increases ($P<0.05$) in serum urea and creatinine concentrations, and significant decreases in sodium and potassium levels when compared with the chloroquine-treated group (group 4). These results confirm that acute administration of chloroquine impairs kidney function and further shows that this renotoxicity is exacerbated when chloroquine is co-administered with paracetamol or with ibuprofen, two common drugs used to manage fever.

Key words: Chloroquine, co-administration, paracetamol, ibuprofen renal toxicity.

INTRODUCTION

Certain drugs such as the aminoglycosides gentamycin and tobramycin, and immuno-suppressive agents such as cyclosporine can be harmful to the kidneys and so require intense monitoring. Many clinicians however are not conscious of the renal damage that may occur with commonly used drugs such as paracetamol, ibuprofen and anti-malarial drugs such as chloroquine.

The therapeutic effect of chloroquine has been shown in its wide use as an anti-malarial agent and in the treatment of rheumatoid arthritis (Ducharme and Farinotti, 1996). Ahmed and his co-workers (2003) showed that chloroquine has pronounced renal actions like marked increase in glomerular filtration rate (GFR), urine flow (diuresis) and sodium excretion rate (natriuresis) accompanied by a reduction in urine osmolarity. Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen have also been shown to significantly reduce prostaglandin E_2 ($PG\text{-}E_2$) synthesis. As a consequence they affect kidney functions and result in such activities like renal vasoconstriction and sodium retention in both man (Bippi and Frolich, 1990) and animals (Colletti et al., 1999). Paracetamol, a common analgesic drug, is reported to be a weak inhibitor of prostaglandin synthesis (Whelton, 1995).

Conventionally, paracetamol, ibuprofen and other NSAIDs are prescribed as anti-pyretic agents to reduce fever and pains associated with common malaria. Hence people living in tropical countries such as Nigeria where malaria is prevalent most often ingest chloroquine co-administrated with paracetamol or with ibuprofen. Chloroquine is also often taken together with ibuprofen in the treatment of rheumatoid arthritis (Bertram, 2001). Since chloroquine has been shown to induce diuresis and natriuresis (Ahmed et al., 2003) and is often co-administered with such drugs as paracetamol and ibuprofen which have also been demonstrated to cause renal impairment by inhibition of prostaglandin synthesis,

*Corresponding authors E-mail: okeyojiako@yahoo.com.

it should be expected that co-administration of chloroquine with either paracetamol or with ibuprofen can cause a pronounced renal dysfunction which may be of clinical significance in patients being treated with these drugs. The aims of this study therefore were to evaluate the renal actions of separately-administered oral chloroquine, paracetamol and ibuprofen in rabbits and to compare such with the renal actions of acute oral chloroquine co-administration with paracetamol and with ibuprofen also in rabbits.

MATERIALS AND METHODS

Animal preparation and drug administration

Thirty six (36) rabbits (New Zealand White) were purchased from the Animal Science Unit of Michael Okpara University of Agriculture, Umudike, Umuahia, Nigeria and were held in the Faculty of Agriculture, Imo State University, Owerri, where they had free access to food (fresh green grass and commercial chicken growers mash) and water. The animals were acclimatized with laboratory conditions for one week and then randomly assigned to 6 groups of 6 animals each. The weight of the animals prior to the study ranged between 1.9 to 2.10 kg.

Paracetamol tablets (Emzor Pharmaceutical Industries Limited, Lagos, Nigeria), chloroquine phosphate tablets (Clarion Medical Limited, London), and ibuprofen (Brustan-N) tablets (Ranbaxy Laboratories Limited, Dewas, India) were purchased from a reputable pharmacy shop in Owerri, Imo State, Nigeria.

Group 1 animals, the control group, received food and water *ad libitum* with no drugs. The other animals received food and water *ad libitum* and in addition group 2 received paracetamol (10 mg/kg body weigth/6 h), group 3 received ibuprofen (20 mg/kg body weight/day), group 4 received chloroquine (5 mg/kg body weight/day), group 5 received chloroquine and paracetamol doses (as above), while group 6 received chloroquine and ibuprofen doses (as above).

The drugs were administered to the animals by oral compulsion for 8 days. On the ninth day 6 ml of blood was collected from the marginal ear vein of each animal using a sterile needle and syringe and transferred into a centrifuge tube, allowed for 30 min to clot before being centrifuged at 2500 g for 5 min using Wisperfuge Model 1384 centrifuge (Tamson, Holland). The supernatant obtained from each was then used for assays.

Biochemical assays

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

Statistical analysis

Results are presented as mean ± standard deviation. The student t-test was used to test significant differences in the results at $P \leq 0.05$.

RESULTS AND DISCUSSION

Table 1 shows the mean values of serum urea and creatinine concentrations in both the test and control groups. The mean values of urea and creatinine showed no significant difference ($p<0.05$) in animals treated with paracetamol or ibuprofen when compared with the values from the control group. Animals treated with chloroquine alone however, showed a significant increase ($p<0.05$) in both urea and creatinine levels when compared with either the control or the other monotherapy groups. The two groups of animals treated with combined therapies (paracetamol + chloroquine) or (ibuprofen + chloroquine) showed significant increases ($p<0.05$) in mean serum urea and creatinine levels when compared with the control or the single therapy groups. There were also significant increases ($p<0.05$) in these parameters in the animals treated with ibuprofen + chloroquine when compared with the values from the animals treated with paracetamol + chloroquine.

A similar trend of results was observed with the mean serum electrolyte concentrations (Table 2). The two groups of animals treated with combined therapies (paracetamol + chloroquine) and (ibuprofen + chloroquine) showed significant depressions ($p<0.05$) in mean sodium and potassium levels when compared with the control or single therapy groups. Also the chloroquine-treated animals showed a significant decrease ($p<0.05$) in sodium and potassium levels when compared with the control, chloroquine or the single therapy groups. There were no significant differences ($p<0.05$) in the mean values of bicarbonate and chloride levels in all the groups of animals.

The results obtained from this study agree with the report of Ahmed et al. (2003) that chloroquine has a natriuretic effect resulting in low levels of serum sodium. The results also show that chloroquine, in addition to this natriuretic (hyponatraemic) effect, has an adverse effect on renal function as evidenced by the high serum urea and creatinine concentrations. The results also show that paracetamol and ibuprofen, on co-administration with chloroquine exacerbate this action. These observations and their pattern of occurrence suggest that chloroquine may have caused the impairment of both glomerular and tubular functions, although the exact mechanisms are not known from the study. The significant reduction ($P<0.05$) in both serum sodium and potassium levels suggests that the levels of sodium and potassium may not have been regulated primarily by the classical membrane-bound Na-K ATPase (Bodermann et al., 1987) and the drug regimen may not have exerted the "sodium shift" theory where the influx of sodium ions into the cell is accompanied by a corresponding efflux of potassium ions into the extracellular fluid (Enwere et al., 2000).

The study also revealed that co-administration of chloroquine with paracetamol or with ibuprofen caused a more pronounced increase in serum urea and creatinine.

Table 1. Mean urea and creatinine levels in test and control groups.

Groups	Urea (mg/dl)	Creatinine (mg/dl)
Control	28.81 ± 2.11	0.68 ± 0.05
Paracetamol	28.72 ± 11.95	0.69 ± 0.08
Ibuprofen	29.71 ± 2.18	0.71 ± 0.05
Chloroquine	36.99 ± 2.26*	0.99 ± 0.07*
Paracetamol + Chloroquine	45.64 ± 2.70**	1.24 ± 0.13**
Ibuprofen + Chloroquine	51.19 ± 2.84***	1.46 ± 0.14***

*Significantly different from control and paracetamol or ibuprofen monotherapy ($p \leq 0.05$
**Significantly different from both control and chloroquine, paracetamol or ibuprofen monotherapy
***Significantly different from control, single therapies and the other combined therapy ($p<0.05$)

Table 2. Mean serum electrolyte levels in test and control groups.

Group	Sodium (mEq/L)	Potassium (mEq/L)	Bicarbonate (mmol/L)	Chloride (mmol/L)
Control	142.09 ± 2.72	3.86 ± 0.24	24.83 ± 1.81	86.01 ± 1.98
Paracetamol	146.68 ± 2.31	4.00. ± 0.39	24.93 ± 2.04	87.67 ± 1.34
Ibuprofen	148.07 ± 2.61	4.05 ± 0.35	24.07 ± 2.31	89.72 ± 1.33
Chloroquine	138.94 ± 1.97*	3.50 ± 0.36**	25.10 ± 1.73	86.54 ± 1.55
Para.+Chloro	134.41± 1.88**	3.32 ± 0.61**	25.33 ± 1.68	85.02 ± 2.69
Ibu.+ Chloro.	138.90± 2.71**	3.51 ± 0.38**	24.23 ± 1.72	87.35 ± 1.90

*Significantly different from control and paracetamol or ibuprofen monotherapy.
**Significantly different from the control, chloroquine, paracetamol or ibuprofen monotherapy.

Our findings have support and may be explained by earlier reports (Marcia, 2000; Colletti et al., 1999) that during renal prostaglandin-dependent states such as cases of dehydration or in diuretic use, administration of drugs that inhibit prostaglandin synthesis like paracetamol or ibuprofen exacerbate renal failure. In people with decreased blood volume or circulation problems, the kidneys depend on the dilating effect of prostaglandins on renal blood vessels for maintenance of renal blood flow. When prostaglandin synthesis is inhibited at this stage, a problem ensues (Marcia, 2000). The observation that animals treated with ibuprofen and chloroquine combined therapy showed a more significant increase in serum urea and creatinine levels may be explained by the fact that ibuprofen is a better inhibitor of prostaglandin synthesis (Colletti et al., 1999).

We conclude therefore that the oral chloroquine administered at recommended dosage, not only has a hyponatraemic effect, but also has an adverse effect on the renal function causing urea and creatinine retention as earlier reported. Further to this, the co-administration of chloroquine with paracetamol or with ibuprofen exacerbates these adverse renal actions of chloroquine. Paracetamol however, has less severe effect on these actions than ibuprofen and so would appear to be a safer analgesic for febrile and malarious patients that are on chloroquine therapy.

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