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Changes in Some Biochemical Parameters of Kidney Functions in Rats Co-Administered with Chloroquine and Aspirin

[1]H.U. Nwanjo, [1]N.J.C. Okolie, [1]G. Oze, [1]M.C. Okafor, [1]D. Nwosu, [2]C. Ajero
[1]B. Anyaehie, [1]G.C. Uloneme, [1]C.J. Njoku and [1]P. Nwamkpa
[1]College of Medicine and Health Sciences,
[2]Department of Animal and Enviormental Biology, Imo State University,
Owerri, Imo State, Nigeria

Abstract: This study was done to establish the effects of co-administration of chloroquine with aspirin on kidney function. We monitored renal parameters such as urea, creatinine and electrolytes. The experimental animals were divided into 4 groups. Group 1 received only food and water (control). Group 2-4 received in addition to food and water either single dose with aspirin (8 mg kg^{-1} body weight day^{-1}), chloroquine phosphate (5 mg kg^{-1} body weight day^{-1}) or combined therapy of chloroquine and aspirin for 8 days. The chloroquine-treated group showed a significant increase in mean serum urea and creatinine levels ($p<0.05$) and significant decrease in mean serum sodium and potassium levels ($p<0.05$) when compared with the corresponding values of the control group. This study also revealed that co-administration of chloroquine and aspirin caused a more pronounced decrease in serum sodium and potassium levels. The results of the study suggest that acute administration of chloroquine may affect kidney function, more so when co-administered with aspirin; two drugs sometimes combined in the treatment of malaria in a malaria endemic country such as Nigeria.

Key words: Chloroquine, aspirin, co-administration, kidney function, biochemical, parameters

INTRODUCTION

The synthetic 4-aminoquinoline drug, chloroquine, was first prepared by Andersag and colleagues in the Bayer Group in 1934 and is still one of the most widely used anti-malaria drugs (Sharma and Nishra, 1999). It is also used clinically to treat rheumatoid arthritis and systemic lupus erythromatosis (Ducharme and Farinotti, 1996). However, increasing evidence suggest that chloroquine may also influence renal function with potentially important consequences for patients whose fluid status is challenged. Ahmed *et al.* (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.

Acetylsalicycllic acid (aspirin) and other Non-Steroidal Anti-Inflammatory Drugs (NSAIDS) such as ibuprofen have been shown to significantly reduce Prostaglandin E_2 ($PG\text{-}E_2$) synthesis and consequently affect kidney functions (i.e., causing renal vasoconstriction and sodium retention, in both man (Bippi and Frolich, 1990) and animals (Colletti *et al.*, 1999). In the kidney, the vasodilatory action of $PG\text{-}E_2$ helps to check the vasoconstrictive activity of the rennin-angiotensin system. This is important to maintain glomerular filtration rate and renal blood flow by modulating the effects of vasoconstrictors, such as angiotensin II or norepinephrine on renal vasculature (Dunn and Zambraski, 1980).

Aspirin irreversibly inhibits the synthesis of prostaglandin and thromboxane via the cyclooxygenase pathway. This makes aspirin different from other NSAIDs such as paracetamol, diclofenac or ibuprofen, which are reversible inhibitors of this enzyme system. Aspirin and other NSAIDs are often prescribed as anti-pyretic agents to reduce fever and pains associated with malaria. Hence people living in tropical countries such as Nigeria where malaria is prevalent are likely to ingest chloroquine co-administered with aspirin. Chloroquine is sometimes given with aspirin in the management of inflammatory conditions, extra intestinal amoebiosis or gout (Issacson *et al.*, 1982) and rheumatoid arthritis (Augustijus and Verbeke, 1993). The current use of low dose aspirin in managing platelet aggregatory diseases and other stroke related conditions are known.

Since chloroquine has been shown to induce diuresis and natriuresis (Ahmed *et al.*, 2003) and is sometimes co-administered with aspirin which has also been demonstrated to cause inhibition of

Corresponding Author: H.U. Nwanjo, College of Medicine and Health Sciences, Imo State University, Owerri, Imo State, Nigeria

renal-protective prostaglandin, it should be expected that co-administration of these drugs may lead to renal dysfunction. This speculation gave rise to the present study, in which we evaluated the renal actions of separately administered oral chloroquine or aspirin and compared these with the renal actions of acute co-administration of the drugs in rats.

MATERIALS AND METHODS

Animals: Twenty four wistar rats were purchased from the Animal Science Unit of Federal University of Technology, Owerri, Nigeria and were held in the Animal House of College of Medicine and Health Sciences, Imo State University, Owerri, where they had free access to food (commercial chicken growers mash, products of Top Feeds Ltd. Sapele, Nigeria) and water. The animals were acclamatized with laboratory conditions for one week. The weight of the animals prior to the study ranged between 200-400 g.

Drugs: Aspirin tablets (Emzor Pharmaceutical Industries Limited, Lagos, Nigeria) and chloroquine phosphate tablets (Clarion Medical Limited, London) were purchased from a standard pharmacy shop in Owerri, Imo State, Nigeria.

Experiment designs: Animals were randomly assigned to 4 experiment groups (n = 6 in each group). Group I animals (control group) received food and water ad libitum with no drugs. The other groups received food and water and in addition group 2 received aspirin (8 mg $kg^{-1}d$), group 3 received chloroquine phosphate (5 mg $kg^{-1}d$) while group 4 received chloroquine phosphate along with aspirin. The drugs were administered to the animals by oral compulsion for 8 d 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, were allowed to stand for about 30 min to clot and further centrifuged at 10,000 rpm for 5 min using Wisperfuge model 1384 Centrifuge (Samson, Holland), serum was separated from clot with Pasteur pipette into sterile serum sample tubes and used for biochemical 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: Statistical evaluation of data was performed by using one-way Analysis of Variance (ANOVA) followed by Duncen's Multiple Range Test (DMRT) (Duncan, 1957).

RESULTS

The changes in the mean values of serum urea and creatinine concentrations in both normal and experimental animals are shown in Table 1. The mean values of urea and creatinine in serum showed no significant difference ($p>0.05$) in animals, treated with aspirin when compared with the values from control group. Animals treated with chloroquine alone, however 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 combined therapy (aspirin + chloroquine) showed significant increase ($p<0.05$) in mean serum urea and creatinine levels when compared with control and the single therapy groups.

Table 2 shows the mean values of serum electrolyte concentrations in both the test and control groups. The chloroquine treated animals showed a significant decrease ($p<0.05$) in sodium and potassium levels when compared with the control group. The animals treated with combined therapy (aspirin + chloroquine) showed significant depressions ($p<0.05$) in mean serum sodium and potassium levels when compared with control or single

Table 1: Mean values of serum urea and creatinine levels in experimental and control groups

Groups	Urea (mg dL^{-1})	Creatinine (mg dL^{-1})
Control	22.52±2.82	0.52±0.02
Aspirin	26.64±3.04	0.58±0.07
Chloroquine	34.26±3.08*	0.96±0.05*
Chloroquine + Aspirin	56.43±4.62**	1.62±0.12**

*Significantly different from control ($p<0.05$), ** Significantly different from control and single therapies ($p<0.05$)

Table 2: Mean values of serum electrolytes in experimental and control groups

Groups	Sodium (mmol L^{-1})	Potassium (mmol L^{-1})	Bicarbonate (mmol L^{-1})	Chlorid (mmol L^{-1})
Control	143.46±2.41	4.20± 0.52	23.80±1.68	87.05±1.38
Aspirin	145.01±2.68	4.06±0.44	24.24±1.84	86.34±1.52
Chloroquine	124.94±3.02*	3.62±0.48*	24.66±2.048	5.98±2.02
Chloroquine + Aspirin	108.42±2.88**	2.42±0.35**	25.06±2.25	86.66±1.78

0* Significantly different from control ($p<0.05$), ** Significantly different from control and single therapies ($p<0.05$)

therapy groups. There was no significant difference ($p>0.05$) in mean values of bicarbonate and chloride levels in all the groups of animals.

DISCUSSION

Serum urea, creatinine and electrolytes (Na^+, K^+, HCO_3^- and Cl^-) are the most sensitive biochemical markers employed in the diagnosis of renal damages because urea and creatinine are excreted through the kidney while the electrolytes are reabsorbed in the tubules. So in cellular damage there will be retention of urea and creatinine in the blood and low reabsorption and excretion of electrolytes by the tubules.

The results obtained in this study confirmed the report of Ahmed *et al.* (2003) that chloroquine has a natriuretic effect resulting in low levels of serum sodium (hyponatraemic effect). In addition to hyponatraemic effect it also significantly reduced ($p<0.05$) serum potassium. This significant reduction suggest that the levels of sodium and potassium may not have been regulated primarily by the classical membrane-bound Na-K ATPase and the drug 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.

Chloroquine administration was also associated with a significant increase in serum urea and creatinine. These observations suggest that chloroquine may have caused both impaired glomerular and tubular functions, although the exact mechanisms are not known from the study. It can be explained by the fact that natriuresis goes together with diuresis, thereby causing dehydration. Dehydration brings about volume depression, which is associated with reduced blood flow and hence low glomerular filtration rate, which results in high plasma urea and creatinine concentration.

This study also revealed that co-administration of chloroquine and aspirin caused a more pronounced increase in serum urea and creatinine levels. This may be explained by earlier reports (Bjorkman, 199; Marcia, 2000; Ojiako and Nwanjo, 2006) that during renal prostaglandin-dependent states such as cases of dehydration or in diuretic use, administration of drugs that inhibit prostaglandin synthesis like NSAIDs (i.e., aspirin, paracetamol, Ibuprofen or diclofenac) exacerbate renal failure. In people with decreased blood volume or circulation problems, kidney depends 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 ensures (Colletti *et al.*, 1999).

CONCLUSION

This study has shown that acute chloroquine administration to rats not only has a hyponatraemic effect but also may result in impaired glomerular and tubular functions causing urea and creatinine retention. Also co-administration of chloroquine and aspirin exacerbates these adverse renal actions of chloroquine. These results suggest that the use of analgesic such as aspirin should be monitored and renal function tests carried out in patients taking chloroquine and other patients under renal prostaglandin dependent state such as dehydration, heat-stress, exercise or a consequence of a disease states such as congestive heart failure or cirrhosis.

REFERENCES

Ahmed, M.H., N. Ashton and R.J. Balment, 2002. The effect of chloroquine on renal function and vasopressin secretion: A nitric oxide dependant effect. J. Pharmacol. Exp. Therapeutics, 304: 156-161.

Andersag, H., 1934. The isoquinoline series. Med-Cham Abh med-cahm forchungsstatten IG Farbenind, 2: 377-383.

Augustijus, P. and N. Verbeke, 1993. Stereoselective pharmacokinetic properties of chloroquine, de -ethyl-chloroquine in humans. Clin. Pharmacokinet, 24: 259-269.

Bippi, H. and J.C. Frodich, 1990. Effects of acetylsalicyclic acid and paracetamol alone and in combination on prostanoid synthesis in man. Br. J. Clin. Pharmacol., 29: 305-310.

Bjorkman, D.J., 1998. The effect of aspirin and NSAIDs on prostaglandins. Am. J. Med., 105: 8-12.

Colletti, A.E, H.W. Vogi, T. Rale, B.J. Zambrask, 1999. Effect of acetaminophen and ibuprofen on renal function in anthestized normal and sodium-depleted dogs. J. Applied Physiol., 86: 592-597.

Ducharme, J. and R. Farinotti, 1996. Clinical pharmacokinetics and metabolism of chloroquine: Focus on recent advancements. Clinical Pharmacokinetics, 31: 257-274.

Duncan, B.D., 1957. Multiple range test for correlated and heteroscedastic means. Biometric, 13: 359 364.

Dunn, M.J. and B.J. Zambraski, 1980. Renal effects of drugs that inhibit prostaglandin synthesis. Kidney Int., 18: 608-622.

Issacson, D., M. Elgart and M.L. Tunner, 1982. Antimalaria in dermatology. Int. J. Dermatol., 21: 379-395.

Marcia, L.B., 2000. Ibuprofen-associated renal toxicity in children. Pediatric Pharmacotherapy, 6: 111-116.

Marshal, W.H., 1957. Urea estimation by thiosemicarbazide method. Am. J. Clin. Pathol., 28: 681-682.

Ojiako, O.A. and H.U. Nwanjo, 2006. Effects of co-administration of chloroquine with paracetamol or ibuprofen on renal function of rabbits, 5: 668-670.

Schales, C. and S.S. schales, 1941. Estimation of serum chloride using mercuric nitrate method. J. Biol. Chem., 140: 879-886.

Sharma, A. and N.C. Mishra, 1999. Inhibition of a protein tyrosine kinase, activity in plasmodium falciparium by chloroquine. Indian J. Biochem. Biophysiol., 36: 299-304.

Tietz, N. W., F.L. Pruden, O. Siggard-Anderson, 1986. Electrolytes, blood gasses and acid base balance. In: Textbook of Clin. Chem. Sounders Philadelphia, pp: 118-1196.