African Journal of Pharmaceutical Research & Development

Vol. 7 No.2 pp.137-141 (2015)

Concomitant use of tea (*Carmellia sinensis*) may inhibit the antimicrobial activity of ciprofloxacin in the treatment of urinary tract infections

Ihekwereme CP[1*], Okoye IE[2], Esimone CO[3], Adikwu MU[4]

[1]Department of Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University, Awka 420281 Nigeria.

[2]Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University, Awka 420281 Nigeria

[3]Department of Pharmaceutical Microbiology and Biotechnology, Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University, Awka, 420281 Nigeria.

[4]Department of Pharmaceutics, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka Nigeria

ABSTRACT

Preclinical studies point to a synergy between tea and ciprofloxacin in the treatment of urinary tract infection. Catechin, an extract of green tea has been demonstrated to act synergistically with ciprofloxacin in murine models against species of *Escherichia coli.* Another study which used urinary isolates of *E. coli* reported synergism, *in vitro* between doses of ciprofloxacin and infusions of tea. In an attempt to evaluate the clinical relevance of these reports, healthy adult volunteers orally received tea and ciprofloxacin simultaneously. A control group received ciprofloxacin only. The ability of the urine samples of volunteers to inhibit the growth of *E. coli in vitro* was used to assess synergism. The result shows that tea reduced the time to reach peak urinary excretion rate, and increased the urinary concentration of the ciprofloxacin. In contrast, tea not only failed to improve bacterial clearance of ciprofloxacin, but also antagonized the antibacterial activity of ciprofloxacin at 1 h and 5 h. This antagonism may likely be due to physical interaction between ciprofloxacin and tea in the gastrointestinal tract. In conclusion, this study shows that co-administration of ciprofloxacin and tea may result in failure in treatment or delay in recovery from urinary tract infections (UTI). Hence, clinicians may have to advise their UTI patients on ciprofloxacin to avoid taking tea during the period of treatment.

KEYWORDS- Drug-Herb Interactions, tea, Urinary tract Infections, ciprofloxacin, *Camellia sinensis*.

INTRODUCTION

Even though a number of preclinical studies have reported synergism between tea (*Camellia sinensis*), or its constituents and ciprofloxacin, there is still need for studies on human subjects [1, 2]. Data from *in vitro* studies on the antimicrobial effects of green tea are promising, but human data are currently lacking [3].

Tea is one of the herbs commonly consumed globally. It is the processed leaves of *Camellia sinensis* plant. *C. sinensis*, the source of black, green, oolong and white teas, is an evergreen shrub indigenous to Southeast Asia. A difference in

***Author for correspondence:** cp.ihekwereme@unizik.edu.ng; +234(0)8034049012

the method of processing of harvested leaves and buds of the plant is responsible for the varieties. White tea is made from very young tea leaves or buds; green tea is made from mature unfermented leaves; Oolong tea from partially fermented leaves; and black tea from fully fermented leaves [4]. Flavonoids and other polyphenols are associated with the health benefits of tea. Catechins, their dimers (theaflavins) and polymers (thearubigins) are abundant in tea [5]. Catechins are considered important for its antimicrobial property. (-)-epicatechin (EC), (-)-epicatechin-3-gallate (ECG), (-)-epigallocatechin (EGC), and (-)-epigallocatechin-3- gallate (EGCG) are the main catechins in tea [4].

There seems to be a conflicting report on the effect of tea on the antimicrobial activity of ciprofloxacin against *E. coli.* There are reports that catechin, a constituent of tea enhances bacterial clearance of uropathogens by ciprofloxacin [1]. However, Esimone *et al* (2007) reported that black tea, *in vitro, antagonize* the antimicrobial activity of ciprofloxacin against the same organism. *Escherichia coli* is an uropathogen commonly found in a majority of urinary tract infections (UTI) [6]. Some of the symptoms of UTI include painful urination, increased urgency, and frequency of urination. The infection can spread and affect the kidney, bladder, urethra, and ureters.

Ciprofloxacin belong to the fluoroquinolone class of antibacterial agent. Other members of the class include enoxacin, gatifloxacin, lomefloxacin, moxifloxacin, ofloxacin, and sparfloxacin. Ciprofloxacin is effective in the treatment of infections caused by Gram-positive and Gram-negative microorganisms. It is primarily used in the treatment of susceptible microorganisms in lower respiratory infections, infections of the skin, urinary tract infections, and sexually transmitted diseases.

Apart from possessing antimicrobial properties, tea has also been reported to enhance activity of some antimicrobial agents. The literature is replete with studies, involving *in vitro* and whole animal models which support these claims [3, 4]. Several review papers have also been published on this [3, 4]. However, it is important to establish the clinical relevance of these studies. In this clinical study, we evaluated how tea affects the elimination of *E. coli* in the treatment of urinary tract infection using ciprofloxacin. The result of the study will serve as guide for clinicians during prescription and patient counseling.

MATERIALS AND METHODS

Study design and subjects

The study was approved by the ethical committee of the University of Nigeria Teaching Hospital, Enugu. Volunteers, who met the eligibility requirements of being non-smoker and not taking any other medicament or alcohol, were selected for the study. All participants granted informed consent for the study. Test group orally received tea and ciprofloxacin simultaneously. A control group received ciprofloxacin only. The ability of the urine samples of volunteers to inhibit the growth of *E. coli in vitro* was used to assess enhancement of antimicrobial activity.

Drug and Herbs

Tea (*Carmellia sinensis*) leaves (LIPTON® tea, Lever Brothers Ltd, Nigeria) were commercial samples of black tea obtained from Nsukka (Nigeria). Ciprofloxacin 500 mg tablets (Cifran®) were purchased from a registered pharmacy in Nsukka, Enugu State Nigeria. The LIPTON® tea was prepared by infusion method by extracting one bag (weight range, 2.20 – 2.25 g) with 180 ml hot water, which was allowed to remain warm before use. The infusion flask was shaken intermittently to aid extraction. At the end of 15 minutes, the infusion was filtered and the residue discarded. The extract was sterilized by autoclaving at 121^{o} C for 15 minutes, and allowed to cool before use.

Drug Administration to Human Volunteers

All volunteers gave their written informed consent for participation in the study. Drug and herb administration was as described by Esimone et al (2013). Two groups (n = 4) of healthy volunteers between 21 – 25 years were recruited. All the subjects fasted overnight prior to drug and herb administration. One group received a single oral dose of 500 mg ciprofloxacin tablet alone with water. The other group swallowed 500 mg ciprofloxacin with about 180 ml of Lipton® tea extract. All the subjects were restricted from food and water for 5 h post-ingestion period. After this period, no attempt was made to restrict food or water intake.

Sample Collection and Assay Technique

Sample collection and assay technique were as previously described [7] for determination of drug excretion rate, urinary concentration-time profile,

cumulative amount of excreted drug and reciprocal urinary inhibitory titer (RUIT). Briefly, at time intervals (0 to 2, 2 to 4, 4 to 6, 6 to 8, and 8 to 24 h), complete void of urine from the subjects were collected. Ciprofloxacin content of urine sample was determined by bioassay using *E. coli* ATCC 11775 as test microorganism.

The urine samples were serially diluted either 2-fold or 10-fold in double strength nutrient broth and sterilized in autoclave at 121^{0}C for 15 minutes. Thereafter, all the sterilized samples were inoculated with 50 to 100 µl of *E. coli* standardized to McFarland 0.5 x 10^{-4}. All the tubes were incubated at 37 ^{0}C for 24 h and then the presence or absence of visible growth was checked and recorded. The Urinary Inhibitory Titre (UIT) was calculated as the highest dilution showing no visible growth.

Data Analysis

RUIT was plotted against time for each regimen. For each subject, a plot of the cumulative amount of Ciprofloxacin excreted in urine against sampling time was made. The amount of Ciprofloxacin recovered from each subject was calculated from the cumulative urinary excretion and the percentage recovery was determined. The results of the test and control groups were compared. All data were analyzed statistically using student's t-test at 5 % of significance. All values are expressed as mean ± standard error of mean.

RESULTS

The result shows the tea affected the urinary excretion rate of ciprofloxacin in a number of ways (Fig. 1A). First, tea reduced the time to reach peak urinary excretion rate from 3 h to 1 h. Second, tea also multiplied the excretion rate of ciprofloxacin by 2 (from 17.72 ± 1.90 to 39.60 ± 4.30), which resulted in an increase in the urinary concentration of the drug (Fig. 1B). We also observed an increase in the cumulative amount of ciprofloxacin excreted (Fig. 1C). However, irrespective of the increased concentration of ciprofloxacin and its accumulation in urine, the RUIT shows tea inhibited the antibacterial activity of ciprofloxacin at 1 h and 5 h (Fig. 2).

DISCUSSION

Tea has been considered the most popular non-alcoholic health beverage in the world [8]. It is commonly consumed for several reasons. A number of persons simply consider it as food, and hence take it alongside treatments for illness. How this affects treatment will be of interest to clinicians. However, successful treatment of urinary tract infection (UTI) will depend on the concentration and duration of exposure of the invading pathogenic organism to the antimicrobial agent. Presence of substances that promote or reduce microbial clearance will affect the clinical outcome of treatment.

The initial rapid increase in the urinary excretion rate of ciprofloxacin (Fig. 1A) is expected to have clinical benefits since it will result in a surge in the urinary concentration of the antimicrobial agent (Fig. 1B). The early arrival of the peak urinary excretion rate together with the increased urinary drug concentration is a desired quality since it suggests a quicker microbial clearance. However, these expectations are not reflected in the RUIT values obtained. There is inhibition of antimicrobial activity at the 1st and 5th hour. This suggests that tea antagonizes bacterial clearance by ciprofloxacin in the urinary tract when the drug and herb are co-administered. The diminished activity recorded in the 1st and 5th hour implies antagonism between tea and ciprofloxacin.

Tea possesses anti-microbial property, and a number of mechanisms of action have been put forward. These include damage to the bacterial cell membrane, inhibition of bacterial type II fatty acid synthesis, and inhibition of bacterial DNA gyrase [9]. Inhibition of DNA gyrase is the same mechanism by which the fluoroquinoloes are thought to act. Since both tea and ciprofloxacin inhibits bacterial DNA, it is expected there would be synergistic or additive effect when both are co-administered. However, the antagonistic effect observed could possibly be due to interaction between both entities. Esimone (2007) reported that ciprofloxacin interacts physically with tea [10]. It is suspected that this interaction, which would be prominent in the gastrointestinal tract, may be responsible for the diminished antimicrobial activity of ciprofloxacin. If this opinion is true, it then suggests also that the serum level of ciprofloxacin when taken together with tea would be low. This would have adverse effect with far reaching consequences.

It is also worthy of note that this inhibition may be associated with conjugated epigallocatechin (EGC) and conjugated epicatechin (EC), which are present

in urine in very large quantities 90 min and 180 min post-ingestion [11]. It is possible that these constituents of tea present in urine interact with excreted ciprofloxacin resulting in inhibition of drug activity.

CONCLUSION

This study shows that co-administration of ciprofloxacin and tea may result in failure in treatment or delay in recovery from UTI. Hence, clinicians may have to advise their UTI patients on ciprofloxacin to avoid taking tea during the period of treatment.

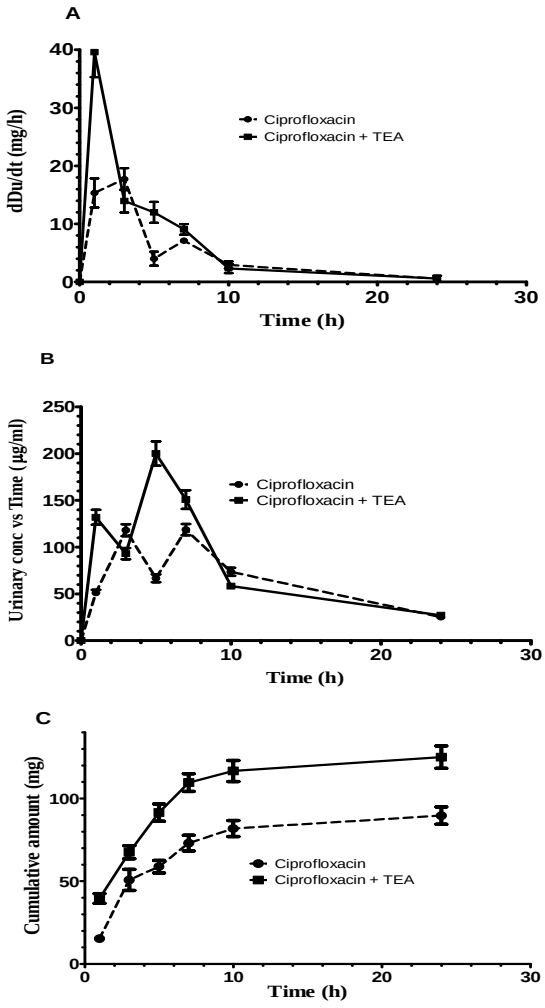

Fig. 1 (A) Excretion rate of Ciprofloxacin in healthy human volunteer. (B) Urinary concentration-time profile of Ciprofloxacin in healthy human volunteers. (C) Cumulative amount of Ciprofloxacin excreted in urine by healthy human volunteers

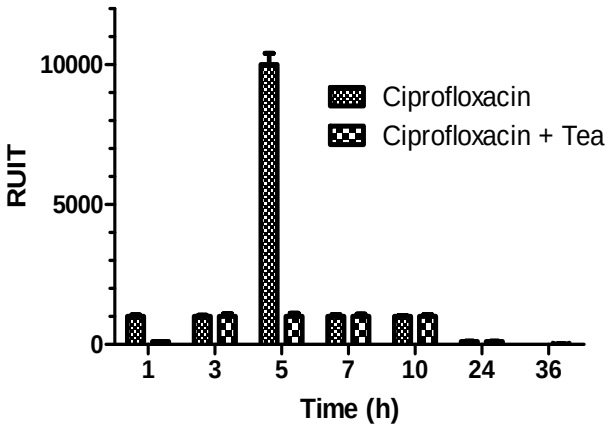

Fig 2. Reciprocal urinary inhibitory titre (RUIT) of ciprofloxacin in the presence of tea

CONFLICT OF INTEREST

The authors alone are responsible for the conduct of this research and in the preparation of the manuscript. The authors declare that there is no conflict of interest

REFERENCES

1. Lee YS, Han CH, Kang SH, Lee S-J, Kim SW, Shin OR, Sim Y-C, Lee S-J, Cho Y-H, Synergistic effect between catechin and ciprofloxacin on chronic bacterial prostatitis rat model, *Int J Urol,* 12, 2005, 383–9.

2. Jazani NH, Zartoshti M, Shahabi S, Yekta Z, Nateghi S, Evaluation of the Synergetic Effect of Water Soluble Extracts of Green Tea (Camellia sinensis) on the Activity of Ciprofloxacin in Urinary Isolated E. coli, *J Biol Sci,* 7, 2007, 1500 – 1503.

3. Noormandi A, Dabaghzadeh F, Effects of green tea on Escherichia coli as a uropathogen, *J Tradit Complement Med*, 5, 2015, 15–20.

4. Reygaert WC, The antimicrobial possibilities of green tea, *Front Microbiol,* 5, 2014, 1–8.

5. Sang S, Lambert JD, Ho CT, Yang CS, The chemistry and biotransformation of tea constituents. *Pharmacol Res*, 64, 2011, 87–99.

6. Reygaert W, Jusufi I, Green tea as an effective antimicrobial for urinary tract infections caused by

Escherichia coli, *Food Microbiol*, 4, 2013, 162.

7. Esimone CO, Ihekwereme CP, Okoye IE, Adikwu MU, Urinary Elimination of Ofloxacin in Humans is Reduced by TEA and Kola nitida Seed, *African J Pharm Sci Pharm*, 4, 2013.

8. Wang X-C, Zhao Q-Y, Ma C-L, Zhang Z-H, Cao H-L, Kong Y-M, Yue C, Hao X-Y, Chen L, Ma J-Q, Jin J-Q, Li X, Yang Y-J, Global transcriptome profiles of Camellia sinensis during cold acclimation, *BMC Genomics*, 14, 2013, 415.

9. Gradisar H, Pristovsek P, Plaper A, Jerala R, Green tea catechins inhibit bacterial DNA gyrase by interaction with its ATP binding site, *J Med Chem,* 50, 2007, 264–271.

10. Esimone CO, Okoli CO, Ayogu CO, In vitro Studies on the Interaction of Tea with Antimicrobial Agents. *Int J Trop Med*, 2, 2007, 63–67.

11. Fung S-T, Ho CK, Choi S-W, Chung W-Y, Benzie IFF, Comparison of catechin profiles in human plasma and urine after single dosing and regular intake of green tea (Camellia sinensis). *Br J Nutr*, 109, 2013, 2199–2207.