Scientific Research and Essay Vol. 2 (11), pp. 482-485, November 2007
Available online at http://www.academicjournals.org/SRE
ISSN 1992-2248 © 2007 Academic Journals

Full Length Research Paper

The effect of a new adaptogen, *Garcinia kola* seed, on the bioavailability of ofloxacin in humans

Charles O. Esimone[1], Chukwuemeka S. Nworu[2]*, Michael U. Adikwu[1], Damian C. Odimegwu[4], Christopher O. Ezugwu[3]

[1]Department of Pharmaceutics, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, 410001, Enugu State, Nigeria.
[2] Department of Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, 410001, Enugu State, Nigeria.
[3] Department of Pharmacognosy, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, 410001, Enugu State, Nigeria.
[4]Department of Pharmaceutical Microbiology, Faculty of Pharmacy, University of Portharcourt, Nigeria.

Accepted 21 September, 2007

***Garcinia kola* seed is a commonly used social masticatory agent in Africa and is believed to possess many useful medicinal properties. The effect of the seed of *G. kola* Heckel on the salivary pharmacokinetics of ofloxacin was studied in healthy human volunteers. In a 2-way crossover design, ten healthy human volunteer received oral dose of 200 mg ofloxacin and saliva samples were collected and analyzed (previous studies have established good correlation between the saliva and serum pharmacokinetics of ofloxacin). After a 2-week washout period, the volunteers again received 200 mg ofloxacin in addition to *G. kola* seeds, and saliva samples were collected and analyzed. The pharmacokinetic studies showed that ingestion of *G. kola* altered ofloxacin pharmacokinetics since it caused significant reductions in C_{max} (6.85 to 5.14 µg/ml), AUC (64.65 to 50.02 µg/h/ml) and K_a (2.53 to 1.58/h) while there was a significant increase in CL_T (69.29 to 86.35 ml/min). A non-significant reduction and increment was recorded for $T_{1/2}$ (1.21 to 0.98 h) and T_{max} (1.2 to 1.7 h) respectively. These data show that *G. kola* impairs the bioavailability of ofloxacin by a possible chelate formation between ofloxacin and flavonoid constituents of *G. kola* seed and by a reduction in the gastric emptying rate.**

Keywords: *Garcinia kola* seed, ofloxacin bioavailability, pharmacokinetic, humans, adaptogen.

INTRODUCTION

Ofloxacin is a fluorinated 4-quinolone carboxylic acid derivative that is readily absorbed in the gastrointestinal tract (Wise et al., 1986; Fu et al, 1992). The drug, like most fluoroquinolones, is active against a wide spectrum of Gram-negative and Gram-positive bacteria. Clinical efficacy of ofloxacin has been documented in patients with respiratory tract infections, upper and lower urinary tract infections, skin and soft tissue infections, gonococcal and non-gonococcal urethritis (Guay et al., 1992). It has been found to particularly inhibit the growth of *Mycobacterium tuberculosis,* the causative organism of lung tuberculosis resistant to isoniazid and rifampicin (Tsukamura, 1985; Kucer and Bennet, 1989)

The *in vivo* efficacy of all drugs is dependent on their bioavailability. For orally administered dosage forms, drug dissolution and/or absorption is a critical determinant and this is usually influenced by pH, gastric emptying rate and exogenous substances present in the gut, among other factors (Labaune, 1989; Proudfoot, 1999). Food-drug interactions generally account for several therapeutic failures of some antibiotics and non-antibiotic drugs (Welling, 1984; Mustafa and Yakasai, 1986; Karee and Okhamafe, 1991; Nwafor et al., 2003).

Mustapha and Yakassai (1986) earlier reported that

*Corresponding author. E-mail: csnworu@yahoo.com, +234 (0) 8033501106.

Pamarindus indica (the major constituent of a local drink commonly consumed in the Northern part of Nigeria) significantly reduced the bioavailability of aspirin in healthy human volunteers. Recently, Nwafor et al (2003) showed that the bioavailability of ciprofloxacin in rabbits is significantly reduced when administered concomitantly with the pulp of unripe plantain (*Musa paradisiaca*). Interaction between food and ampicillin has been shown to reduce their systemic availability by lowering gastric pH and delaying gastric emptying time (Welling, 1984). Ofloxacin, like other fluoroquinolones undergo pharmacokinetic interaction with exogenous materials such as polyvalent cations from antacids and dairy food (Shiba et al., 1982; Akerele and Okhamafe, 1991; Kivisto et al., 1992) which lead to a reduction in their bioavailability.

G. kola seed, known in commerce as "bitter cola" is popular in African traditional medicine, where it is usually used to treat throat infections, cough and stomach upset (Hussain et al., 1982; Iwu and Igboko, 1986; Igoko, 1986; Middleton and Kandaswani, 1991; Iwu, 1999; Meserole, 1999). Recently, its applicability as an adaptogen (rejuvenating, stimulating and/or anti-stress agent) has been reported (Iwu, 1999; Esimone et al, 2007). In this respect, the seed, which is edible, has been shown to help organisms to adapt to stress by influencing multiple regulatory systems responsible for stimulus-response coupling such as the immune system (Iwu, 1999; Meserole, 1999; Esimone et al., 2007). Bitter cola seeds have been shown to contain a complex mixture of biflavonoids, prenylated benzophenones and xanthones which account for the majority of its effect (Hussain et al., 1982; Iwu and Igboko, 1986; Igoko, 1986). These effects include antiviral, anti-inflammatory, antidiabetic, bronchodilator and antihepatotoxic properties. Some proprietary dietary supplements containing *G. kola* extractives already exist in US and African markets (Iwu, 1999, Meserole, 1999).

In Nigeria, it is chewed habitually for social reasons, for oral hygiene and as a masticatory agent (Meserole, 1999). Our observation in most parts of Nigeria is that sometimes, patients on antibiotic therapy also chew bitter cola habitually or because of its traditionally acclaimed anti-infective properties. We have recently demonstrated that the bioavailability of ciprofloxacin in rabbit is significantly reduced by concurrent administration of *G. kola* seed (Esimone et al., 2002a) and that due to extensive adsorption of ciprofloxacin by *G. kola*; the latter could be used as an alternative antidote against ciprofloxacin poisoning (Esimone et al., 2002b). In an attempt to extend such a study in humans, we have chosen another 4-fluoroquinolones, ofloxacin, whose salivary pharmacokinetics has been previously established to correlate well with the serum pharmacokinetics (Okhamafe et al., 1996). It is therefore the objective of this study to evaluate the possible effect of such concomitant ingestion of *G.kola* seed and ofloxacin on the bioavailability of ofloxacin in humans.

MATERIALS AND METHODS

Ten healthy male volunteers, aged between 20 - 30 years and with mean body weight of 63.3 ± 4.02 kg, provided informed consent for the study which was approved by our institution's ethical committee. They were non-smokers and did not ingest any medicine, alcohol/alcoholic beverages in the preceding fortnight and throughout the duration of the study. The volunteers fasted from midnight of the night preceding dosing until 4 h post dosing of the drug, ofloxacin (Tarivid® - Hoechst Nigeria PLC). In a two-way crossover design, the volunteers received 200 mg ofloxacin tablet with 180 ml of distilled water, and after two weeks washout period, the subjects received two seeds of *G. kola* each 30 min before the 200 mg ofloxacin tablet with the same quantity of water. The G. *kola* seeds with weight range of 2.5 - 3.3 g were purchased from local market in Nsukka, Nigeria. From each of the volunteers, and in each case, saliva samples were collected in clean test tubes at 0.5, 1.0, 2.0, 3.0, 4.0, 5.0 and 24.0 h period. The samples were stored in the freezer until analyzed.

Blank saliva were first collected from volunteers, centrifuged at 3000 x g for 20 min and the supernatant diluted with distilled water and used to prepare standard samples of ofloxacin containing 0.625, 1.25, 2.50, 5.00 and 10.00 mg/l. The absorbances were determined with UV-spectrophotometer at 283 nm. The concentrations of ofloxacin in saliva samples when administered alone and concurrently with *G. kola* seeds were determined from the calibrated curve. The area under saliva drug concentration versus time curve was calculated using a linear trapezoidal estimation.

Analysis of data

In analyzing the data, it was assumed that ofloxacin elimination followed first-order kinetic at all concentrations encountered. Results were expressed as mean ± standard error of mean. The significance of the difference between means of data collected when ofloxacin was given alone and when it was given concurrently with *G. kola* seed was determined using the Student's t test and results were regarded as significant at $P<0.05$.

RESULTS AND DISCUSSION

The effect of *G. kola* seed (GKS) on ofloxacin (OFX) pharmacokinetic in the healthy human volunteers is shown in Table 1. From the results, it appears that the average bioavailability of OFX was significantly reduced when it was concurrently administered with GKS. The area under the saliva concentration-time curve (AUC), the maximum salivary concentration (C_{max}) and the absorption constant of ofloxacin were significantly decreased ($P<0.05$) when the volunteers ingested the GKS. This impairment in bioavailability could be attributed to two factors. In the first instance, GKS has been reported to reduce gastric motility (Igboko, 1986). Ofloxacin, like all fluoroquinolones, is favorably absorbed in the small intestine; therefore, its absorption will be directly affected by gastric emptying rate (Proudfoot, 1999). This assertion is clearly highlighted by the significant reduction in absorption rate of OFX in the presence of GKS (2.53 to 1.58 h^{-1}). Moreover, conventionally, ofloxacin tablet is usually film-coated in order to shield it from the very low gastric pH, which could possibly lead to degradation of

Table 1. Pharmacokinetic parameters of ofloxacin alone and with *G. kola*.

Parameter	Subjects on ofloxacin and *G. kola*	Subjects on ofloxacin alone
C_{max} (µg/ml)	5.14 ± 2.57	6.85 ± 3.43
T_{max} (h)	1.70 ± 1.40	1.20 ± 0.45
$T_{1/2}$(h)	0.98 ± 0.32	1.21 ± 0.50
K_a (h^{-1})	1.58 ± 0.77	2.53 ± 1.29
$AUC_{0\text{-}24h}$(µg /h/ml)	50.02 ± 24.97	64.65 ± 40.50
Total salivary clearance Cs (ml/min)	86.34 ± 50.59	69.29 ± 44.65

the drug. Thus, long gastric resident time is not very desirable for favorable bioavailability of ofloxacin.

Secondly, the impaired absorption of OFX could be as a result of chemical interaction between OFX and the chemical constituents of GKS. GKS consist mainly of flavonoids (Iwu and Igboko, 1986; Igoko, 1986). Flavonoids are known to possess certain functional groups (such as C=O, C=C, etc), which aid them in forming various intermolecular complexes with a variety of compounds. They form chelates, possess anti-oxidant properties and affect cellular protein phosphorylation (Middleton and Kandaswami, 1991). Our previous studies have also revealed that GKS contains metallic ions like aluminum, magnesium, calcium and copper (Esimone et al., 2003), which are known to form unabsorbable complexes with fluoroquinolones (Shiba et al., 1982; Akerele and Okhamafe, 1991; Kivisto et al., 1992; Esimone et al., 2002). Such complex (chelate) formation is usually very stable and involves the 3-carboxyl- and 4-oxo substituents of ciprofloxacin or the 4-oxo substituents of ofloxacin (Shiba et al., 1982). The complexed form of the drug is usually unabsorbable, with the result that the maximum amount of drug absorbed (C_{max}) and the total (cumulative) quantity of drug absorbed (AUC) will be reduced when the drug is complexed. This is particularly true for stable drug complexes. Therefore, the significant reduction in C_{max} and AUC of OFX in the presence of GKS suggests a possible complex formation between ofloxacin and the constituents of GKS especially in the light of the fact that the major constituents of GKS (flavonoids and metallic ions) are known to form molecular complexes with a wide variety of agents, including fluoroquinolones. Moreover, our previous *in vitro* studies (Esimone et al., 2003) further revealed that this herb-drug interaction between ofloxacin and GKS could have some pronounced pharmacodynamic influence because it was observed that the antimicrobial activity (*in vitro* pharmacodynamic effect) of ofloxacin is significantly reduced in the presence of GKS extracts.

Even though there was a non-significant decrease in half-life ($T_{1/2}$), the significant increase in total clearance (C_T) suggests an increase in OFX metabolism in the presence of GKS. Since flavonoids have been shown to activate and induce the synthesis of the primary enzyme systems that are involved in the metabolism of various drugs and xenobiotics (Middleton and Kandaswami, 1991), it is possible that activation/inducement of liver metabolism enzymes is involved in the rapid elimination of OFX in the presence of GKS.

The observed reduced bioavailability of ofloxacin when taken concomitantly with *G. kola* seed has some therapeutic implications especially when treating infections caused by slightly sensitive (moderately resistant) strains of bacteria. For such bacteria strains, the MIC of ofloxacin may slightly exceed $5.0\mu g/ml$ which is just about the maximum concentration ofloxacin achieved (C_{max}) in the presence of *G. kola*. This could result in microbial survival, spread of resistance and hence therapeutic failure.

Conclusion

Our results indicate that *G. kola* seeds exhibited significant pharmacokinetic interaction with ofloxacin, which results in reduced bioavailability of the drug. It is therefore advisable that patients on ofloxacin antibiotic should abstain from consuming *G. kola* seed concomitantly.

ACKNOWLEDGEMENT

Financial support from the University of Nigeria Research Grant Committee to Dr. C.O. Esimone (research grant # 94/283) is gratefully acknowledged.

REFERENCES

Akerele JO, Okhamafe AO (1991). Influence of oral co-administered metallic drugs on ofloxacin pharmacokinetics J Antimicrob Chemother; 28: 87-94.

Fu KP, Lapredo C, Foleno B, Isaacson DM (1992). *In vivo* and *in vitro* antibacterial activities of levofloxacin, an optically active ofloxacin. J Antimicrob Agents Chemother; 36: 860-866.

Esimone CO, Nwafor SV, Okoli CO, Chah KF, Uzuegbu DB, Chibudu C, Eche MA, Adikwu MU (2002a). *In vivo* evaluation of interaction between aqueous seed extract of *Garcinia kola* Heckel and ciprofloxacin hydrochloride, Am J Therapeutics; 9: 275-280.

Esimone CO, Adikwu MU, Ibezim EC, Ofoefule SI, Nwafor SV, Onuoha OM (2002b). Potential application of *Garcinia kola* seed as a natural antidote in the management of ciprofloxacin hydrochloride poison: an *in vitro* study. Acta Pharmaceutica; 52: 219-226

Esimone CO, Adikwu MU, Ndu OO, Udeogaranya PO, Ezeugwu CO, Obonga W (2003). Effect of *Garcinia kola* seed extract on the antimicrobial properties of some antibiotics in-vitro. J. Pharmaceutic. Allied Sci. 2: 114-120.

Esimone CO, Adikwu MU, Nworu CS, Okoye FBC, Odimegwu DC (2007). Adaptogenic potentials of *Camellia sinensis* leaves, *Garcinia kola* and *Kola nitida* seeds. Sci. Res. Essays, 2(7) :232-237.

Guay DRP, Opasli JA, Mahou PG, Varges R, Matzke GR, Flor S (1992). Safety and pharmacokinetic of multiple doses of intravenous ofloxacin in healthy human volunteers. J Antimicrob Agent Chemother; 36: 308-312.

Hussain RA, Owegby AG Parimoo P, Eatomam PG (1982). Kolanone, a novel polyisoprenylated benzophenone with antimicrobial properties from fruit of *Garcinia kola*. J Med Plant Res, 44: 78-81.

Igboko AO (1986). The anti-inflammatory and other properties of the constituents of Garcinia kola Heckel. A dissertation submitted to the Deparment of Pharmacognosy University of Nigeria, Nsukka, in fulfillment for the award of Ph.D.

Iwu MM, Igboko AO (1986). The flavonoids of *Garcinia kola*. J Natural Prod , 45: 650-651.

Iwu M (1999). *Garcinia kola*: a new adaptogen with remarkable immunostimulant, antiinfective and anti-inflammatory properties. A colloquim on *Garcinia kola* presented in International Conference on Ethnomedicine and Drug Discovery, November 3-5, 1999, Maryland, USA, PL-26.

Kivisto KP, Ojala-Karlson P, Neuvonon PJ (1992). Inhibition of norfloxacin absorption by dairy products. J Antimicrob Agent Chemother; 36: 489-491.

Kucer A, Bennett M (1989). The use of antibiotics: A comprehensive review with clinical emphasis: 4th ed., H.M.B Oxford, 1989: 1264-1266.

Labaune JP (1989). Handbook of Pharmacokinetic toxicity assessment of chemicals, Ellis Horwood Pub, 569-647.

Meserole L (1999). *Garcinia kola* in clinical therapeutics – present and potential indications as a tonic and therapeutic medicine. A colloquim on *Garcinia kola* presented in International Conference on Ethnomedicine and Drug Discovery, November 3-5, Maryland, USA. PL-27.

Middleton E, Kandaswami C (1991). The impact of plant flavonoids on mammalian biology: implications for immunity and cancer. In Harborne JB (Ed): *The flavonoids:* advances in research since 1986 Chapman and Hall, London, 619-652.

Mustafa A, Yakasai IA (1986). Effect of *Pamarindus indica* L. on the bioavailability of aspirin in healthy human volunteers. Eur. J. Drug Metab. Pharmacokinet; 21: 223-226.

Nwafor SV, Esimone CO, Amadi CA, Nworu CS (2003). *In vivo* interaction between ciprofloxacin hydrochloride and the pulp of unripe plantain (*Musa paradisiaca*). Eur. J. Drug Metab. Pharmacokinet, ; 28: 253–258.

Okhamafe AO, Akerele JO, Aigbavboa SO, Okei EA (1996). Trial rectal formulation of ofloxacin: preliminary pharmacokinetics in the healthy human volunteers, J West Afr Pharm; 10: 17-20.

Proudfoot SG (1999). Factors influencing bioavailability: factors influencing absorption from the gastrointestinal tract. In: Pharmaceutics, the science of dosage form designs (Ed. Aulton ME) Churchill Livingston, London; 135-137.

Shiba K, Sakai O, Shimada J, Okazaki A, Hakusue H (1982). Effects of antacids, ferrous sulphate and ranitidine on absorption of DR-3355 in humans. J Antimicrob Agent Chemother; 36: 2270-2274.

Tsukamura M (1985). *In vitro* antituberculosis activity of a new antibacterial substance, ofloxacin (DL 8280). Amer. Rev. Respir. Dis. B: 348

Welling PG (1984). Interaction affecting drug absorption. Clin Pharmacokinetic; 9: 404.

Wise R, Lister R, McNulty CAM Griggs D, Andrews JM (1986). The comparative pharmacokinetics of five quinolones. J. Antimicrob. Chemother. 18: (suppl.D) 71-81.