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Studies on the effect of trikatu on oral bioavailability of ciprofloxacin and ofloxacin

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ABSTRACT

Ciprofloxacin and Ofloxacin are used to treat variety of Bacterial infections in Humans. These two drugs possess poor oral bioavailability as found from literatures. Ayurvedic literatures deal with the enhancement of oral bioavailability by TRIKATU (mixture of alcoholic extracts of dried fruits of Piper longum, dried fruits of Piper nigrum and dried rhizomes of Zingiber officinalis). The study was aimed to find out the efficacy of TRIKATU or its components in enhancing bioavailability of the above antibiotics. The extracts of components of TRIKATU were preparedby soxhlation using alcohol (90%). The study was carried out in rabbits by oral administration of the extracts of the components and their combination in equal proportions (TRIKATU) along with above antibiotics. Blood samples were drawn at time intervals equal to three half – lives of the antibiotics and their plasma concentrations were estimated microbiologically. TRIKATU enhanced the Bioavailability of Ciprofloxacin, but the components produced no effect on Ofloxacin Bioavailability. Trikatu has shown maximal enhancementfor both antibiotics

Keywords: TRIKATU, Bioavailability, Ciprofloxacin, Ofloxacin

INTRODUCTION

Ayurveda means the "Science of life"; the chief source of Indian medicine, has been reused now a days instead of allopathy. This is because of large portion of Indian population are in rural areas covered under the herbal medicinal sources. When we combine ayurveda with allopathy it shows a miraculous consequence [1]. "Trikatu" the three acrids used very frequently in Ayurveda; is the combination of common culinary herbals like Black Pepper (*Piper nigrum* Linn.), Long Pepper (*Piper longum* Linn.) and Ginger (*Zingiber officinalis* Rose.). The evidence of use of these came out with report stating their effect on oral bioavailability of the drugs with which they are combined [2- 4].Literatures reveal that its individual components enhance the bioavailability of many drugs [2-4]. Though Ciprofloxacin and Ofloxacin are extensively used in treating various infections, they have problems in their oral bioavailability [5]. The oral bioavailability of Ciprofloxacin is 70% and that of Ofloxacin is 100%.This study was aimed to find out the efficacy of "Trikatu" and its individual components in enhancing oral bioavailability of Ciprofloxacin and Ofloxacin using animal models(Rabbits).

MATERIALS AND METHODS

The components of Trikatu namely, the dried fruits of Black Pepper (*Piper nigrum* Linn.), Long Pepper (*Piper longum* Linn.) and the dried rhizomes of Ginger (*Zingiber officinalis* Rose) were procured from M/s Indian Medical Practitioners Co-operative Stores (IMCOPS), Chennai and their Pharmacognostical characters were ascertained The Antibiotics were purchased from Madras pharmaceuticals, Chennai and the samples were found to comply with specifications as per Indian Pharmacopoeia [7]. The test microorganism; *Bacillus subtilis* (ATC 6633) was obtained from M/S Caplin Point Lab(p) Ltd ,Pondicherry . The Culture and Assay Media were supplied by M/S Hi-Media Ltd., Mumbai. The alcoholic extracts were prepared by Soxhlation, using alcohol (90%) as solvent [2,3]. The rabbits of either sex were procured from the Animal House of Rajah muthiah medical college. The animals were maintained in a diet and quantity of water as prescribed by Central animal house, Rajah Muthiah Medical College and Hospital, Annamalai University and were housed at ambient temperature (25±1ºC). The Plasma concentrations of Ciprofloxacin and Ofloxacin were determined microbiologically (Filter paper disc–diffusion assay) using *Bacillus subtitlis* (ATCC 6633) as test organism [8,9]. Peak plasma concentration (*C* max) and time to reach the peak

plasma concentration (*T*max) were calculated from the actual plasma data. The Elimination rate constant (K el) was calculated by regression analysis of the mono exponential declining line of the log plasma drug concentration versus time graph (10), while elimination half life (*t*1/2el) was obtained from the formula *t*1/2el=0.693/: K el. Absorption rate constant (*K*a) was calculated by the method of residuals. The Area under Curve (AUC) was determined by Trapezoidal rule [11]. Extension of the AUC data to infinity (AUC) was done by dividing the last observed concentration of drug in plasma by K el. Relative bioavailability (Fr) was calculated by dividing the AUC of tests (antibiotics + adjuvants) by AUC of Standard (antibiotics alone). The significance between respective treatment group was calculated by using a paired student's 't' test.

Experimental Design

For animal studies the dried extracts were suspended in water by using CMC (1%) as suspending agent and sodium benzoate (1%) as preservative [2]. TRIKATU suspensions were made by mixing equal parts by weight of each suspensions containing 30 mg residue in each suspension. 2 groups of male rabbits (6 rabbits/group) weighing 1.5 – 2.0 kg were fasted overnight. Eachrabbit group was administered with drug and adjuvants through intra-gastric tube, as per the following table.

Rabbits Group No.	Drug	Adjuvant
I	Antibiotic body weight (150mg/kg	No adjuvant (Control)
II	Antibiotic body weight) (150mg/kg	Suspension TRIKATUof (45mg/kg)

After administration of antibiotics with and without adjuvants, each rabbit was fed with 120 ml water. Exactly 0.5 ml of blood samples were collected from the ear veins of rabbits using sterile syringes at time intervals equal to 3 half –lives of drugs (Ciprofloxacin- t½-3-5to4-5 hrs; ofloxacin 5-8 hrs)[5] and then transferred to sterile eppendorffs (2ml capacity) containing 1 µl of sterile anticoagulant solution (10%w/v sodium citrate).The plasma was separated by centrifuging blood samples at 2000rpm for 20minutes.The above procedure was approved by Institutional Animal ethics Committee (IAEC), (Registration No.160/1999/CPSEA), of Rajah Muthiah Medical College & Hospital, Annamalai University. The plasma concentrations of antibiotics were determined microbiologically.

RESULTS AND DISCUSSION

Effect of TRIKATU on oral bioavailability of Ciprofloxacin

As Fig.1 & Table 1 convey that there was a definite increase in bioavailability of Ciprofloxacin on co administration with Trikatu and its individual components. The enhancement of bioavailability of Ciprofloxacin was 178% by Trikatu. Trikatu produced maximal bioenhancement of oral bioavailability of Ciprofloxacin. All the data fitted to one compartment model with first order kinetics. The enhancement may be due to the action of piperine present in *Piper nigrum* and in *Piper longum* and may be due to an unknown principle in *Zingiber officinalis.* Trikatu produced an additive effect.

Table: 1 Effect of TRIKATU on oral Bioavailability of Ciprofloxacin

S. No	Drug	Cmax (µg/ml)	Tm ax in hrs	T ½ (in hrs)	AUC (µg- hr/ml)	AUC *α* (µg-hr/m l)	Ke
1	Ciprofloxacin	15.42±0.42	10±0.098	2.6±0.12	105.54±O.32	21.46±0.98	0.266±0.042
2	Ciprofloxacin + TRIKA TU	30.25±0.68	1.05±0.12	2.6±0.15	188.02±0.46	26.27±1.12	0.263±0.026

P> 0.05

Fig 2: Effect of blood samples of Ciprofloxacin with TRIKATU against Bacillus subtilis

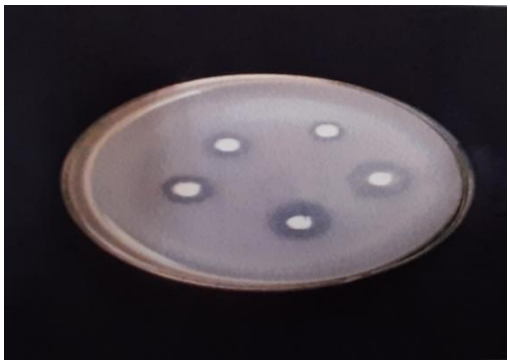
Effect of Trikatu on oral bioavailability of Ofloxacin

As Fig-2 & Tab-2 show that there is slight increase in bioavailability with co-administration of Ofloxacin along with Trikatu (174%). All the data fitted to one compartment model with first order kinetics. Here also the enhancement of bioavailability by Trikatu was due to additive effect.

Table 2: Effect of Trikatu on oral bioavailability of Ofloxacin

S.N O	Drug	Cmax (µg/ml)	Tm ax in hrs	T ½ (in hrs)	AU C (µg- hr/ ml)	AU Cα (µg- hr/ ml)	Ke
1	Ofloxacin	16.52±0.30	4.02±0.56	4.40±0.26	160±0.26	33.52± 0.89	0.157±0.021
2	Ofloxacin + TRIKATU	34.92±0.42	4.82±0.56	5.20±0.42	280.05±0.42	52.25± 0.89	0.133±0.025

Fig 2: Effect of blood samples of Ofloxacin with TRIKATU against Bacillus subtilis



CONCLUSION

TRIKATU the combination of three acids used in Ayurveda increased the bioavailability of Ciprofloxacin and Ofloxacin when co-administered. The study assumes importance in the light of reports stating that Trikatu reduced the bioavailability of Rifampicin. Since Ciprofloxacin and ofloxacin are currently used to treat many bacterial infections, their improved bioavailability through oral route can eliminate the need to administer them by more painful parenteral routes, thus eliminating risk of hypersensitivity. The doses of Ciprofloxacin and Ofloxacin can be reduced, which may lead to reduction in dose related side effects and infectious diseases and improved patient compliance.

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