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The Effect of *Brassica Oleracea* (Cabbage) on The Pharmacokinetics of Ciprofloxacin in an Animal Model

Amani Sa`adeh[1], Talal Aburjai[1], Nasr Shraim[2], Mutasim Al-Ghazawi[1 *]

[1] School of Pharmacy, The University of Jordan, Amman, Jordan
[2] Department of Pharmacy, Faculty of Medicine and Health Sciences, An-Najah National University, Nablus, Palestine.

ABSTRACT

The effect of *Brassica oleracea* (Cabbage) on the pharmacokinetics of ciprofloxacin was studied in rabbits. A single dose of Ciprofloxacin (40mg/kg) was given to rabbits as a suspension along with an aqueous extract of *Brassica oleracea (*var. *capitata)* equivalent to 2g/kg. Twelve rabbits were sampled in a two-period, two-sequence, crossover study, with 7day washout period. Blood samples were obtained at (t = 0, 5, 15, 25, 40, 60, 90, 120, 180, 240, 360, 480 and 580 minutes), and analyzed using a validated HPLC method. A reversed phase high performance liquid chromatographic method (RP-18) was used for the determination and quantification of plasma ciprofloxacin concentrations. The minimum quantifiable concentration of ciprofloxacin was 6 ng/ml (LOQ), the limit of detection (LOD) was 2 ng/ml, and calibration curves were linear over the range 0.01-8.0 µg/ml, with correlation coefficients >0.999. Both, the between-day coefficient of variation (interday RSD) and within-day coefficient of variation (intraday RSD) for quality-control samples were less than 5%. The pharmacokinetic values for ciprofloxacin were estimated by noncompartmental methods. When co-administered with the cabbage extract, T_{max} for ciprofloxacin in plasma was reduced to the half; C_{max} was increased by 1.5 times and AUC was 1.32 times higher. Results obtained indicated a potentiating effect of *Brassica oleracea* (Cabbage) on the ciprofloxacin which could be a result of the effect of glucosinolate and brassicasterol found in cabbage.

Keywords: Brassica Olearacea, Cabbage, Ciprofloxacin, Rabbit.

1. INTRODUCTION

Recently, the interest in botanical medicine has increased tremendously.[1] Little data is available that documents the safety and effectiveness of combining herbs and prescription drugs. However, some possible interactions is that one substance would alter the clinical effectiveness or bioavailability of another when co-administered resulting in increase or decrease in the effect of either or both.[2,3,4,5]

Interactions between ciprofloxacin and other non-antibiotic agents occur.[6,7,8] Some can be predicted from in vitro results, general pharmacodynamics rules, and from the fact that ciprofloxacin is an inhibitor of CYP1A2 in the liver, whereas other interactions appear to be unpredictable. [9,10] Currently, the only clinically significant interactions are the inactivation of ciprofloxacin by antacids and an increase in theophylline and caffeine blood levels (substrates of the CYP1A2). Possible influences of edible plants we routinely ingest have not been thoroughly investigated. [11,12,13,14,15]

Ciprofloxacin is a synthetic broad spectrum antimicrobial agent. It is a member of the second generation of the fluoroquinolones, rapidly and well absorbed from the gastrointestinal tract after oral administration, the bactericidal action of ciprofloxacin results from inhibition of the enzyme DNA gyrase.[16]

Cabbage belongs to the Cruciferae family, and it is native to the Mediterranean region of Europe, and has

* alghazam@ju.edu.jo
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many varieties of the same plant, *Brassica oleracea*.[17]

White cabbage supplies many nutrients like potassium, sodium, calcium, magnesium, iron, phosphorus, sulfur, silicon and chlorine. [18] In one cup of cabbage we find 1 gram of protein, 5 grams of carbohydrates, 46 mg of calcium, 0.5 mg of iron, 50 mg of ascorbic acid, 0.3 mg of niacin, 0.05 and 0.06 mg of riboflavin and thiamine, respectively. Also, it contains trace fat, water content of about 92% and vitamin A value of about 80 IU. Cabbage contains S-methyl cysteine sulfoxide. Cabbage characteristic aroma is due to the presence of thioglucosides (Glucosinolates), anionic glycosides known as (cabbage glucobrassicin). It consists of a glucose residue, a sulphate group and an aglycone, and the molecule occurs as a potassium salt. It also contains brassicasterol. Formation of thiocyanates is possible in cabbage when bruised by the action of the enzyme thioglucosidase or myrosinase. [19,20]

The aim of the present study is to evaluate any possible pharmacokinetic interactions between ciprofloxacin and *Brassica oleracea* L. var. *capitata* (Cabbage). This plant was chosen in this study since it is widely used as an edible vegetable and it is known to have high concentrations of minerals and potential beneficial medicinal agents.

Materials and methods

Animals

Twelve rabbits were used in this study (average weight 1.8-3.8kg) 6 females and 6 males. An appropriate species with suitable biological characteristics were chosen, including behavioral characteristics, genetic constitution, nutritional, microbiological and general health status.[21,22] Animals were handled with care and consideration in accordance with the rules of the institution (Animal Housing, Faculty of Medicine, and University of Jordan).

Drugs

Ciprofloxacin hydrochloride was kindly provided by the Jordanian Pharmaceutical Company (JPM) and Enrofloxacin was kindly provided by the Arab veterinary industrial company (AVICO), and was employed as an internal standard in the high performance liquid chromatography (HPLC) assay. Cabbage was purchased from the local market and was authenticated by macroscopic examination and microscopic identification at the Pharmacognosy laboratory at the School of Pharmacy, University of Jordan.

Experimental design

The design was a two-period, two-sequence, crossover study, with 7- day washout period. Animals were divided into two groups; Group A and group B. group A was given a single dose ciprofloxacin suspension (control group). Group B was given ciprofloxacin along with the extract of the cabbage (test group). Rabbits were kept in good housing conditions, and were fasting overnight. At the sampling day, a fixed amount of cabbage (250g) was macerated in 500 ml of hot boiled de-ionized water for one hour. Rabbits were given 10 ml of the cabbage extract by intubation, followed within 10 minutes by the ciprofloxacin suspension (125mg/ml). Blood samples (2 mL) were drawn from the rabbit`s ear at each time and were transferred into K3-EDTA tubes. The blood samples were then centrifuged at 4000 rpm for 10 minutes and 0.5 ml of plasma was used in analysis. Blood samples were withdrawn at appropriate times for appropriate time intervals (t = 0, 5, 15, 25, 40, 60, 90, 120, 180, 240, 360, 480 and 580 minutes). Sampling of rabbits was performed in the Animal Housing, School of Medicine, The University of Jordan.

High-performance Liquid Chromatographic Assay

A highly sensitive, accurate and reproducible HPLC method for the determination of ciprofloxacin in plasma was developed based on previously reported procedures.[23] Different mobile phases, plasma preparation procedures and flow rates were tried during method optimization.

The HPLC system was a Shimadzu Class-VP System consisting of a SIL-10ADVP autosampler, a LC-10ADVP pump, a DGE-14A degasser, a SCL-10ADVP controller and a RF-10AXL fluorescence detector. Chromatographic separation was achieved using a reversed phase C18 column (MetaChem polaris 5 µ C18-

A 250 x 4.6mm). For fluorescence detection, the excitation wavelength was set at 280 nm and the emission wavelength was 442 nm.

Ciprofloxacin stock solution (100µg/ml) was prepared by dissolving 20 mg of ciprofloxacin hydrochloride in 200 ml of bi-distilled water.

Separation was excellent and retention times were 16.6 and 23.5 min for Ciprofloxacin and Enrofloxacin, respectively.

Sample preparation

Plasma samples were prepared by the addition of 200 µl of plasma to 200 µl of stock solution of ciprofloxacin (0.5, 1, 2 µg/ml) then 400µl of acetonitrile were added to precipitate proteins. Samples were vortex mixed for two minutes, then centrifuged at 3500 rpm for 15 minutes.

The supernatant was evaporated under nitrogen stream at 45 C, then the residue was reconstituted with 200 µl of the internal standard (1µg/ml) solution. 20 µl of the reconstituted solution were injected into the chromatographic column.

Pharmacokinetic and Statistical analysis

All Pharmacokinetic analysis was performed using WinNonlin professional (version 4.0.1, Pharsight Inc., Cary, NC).The pharmacokinetic values for ciprofloxacin were estimated by Non-Compartmental methods. Values for peak concentration (Cmax) and time to Cmax (t max) were obtained directly from the observed data. Concentration versus time profiles were plotted for each rabbit, and the terminal disposition rate constant λz was determined by the log linear regression of at least three data points judged to be in the terminal phase. The terminal phase half-life was determined by dividing 0.693 / λz.

Statistical comparisons of the estimated pharmacokinetic values were performed by Analysis of Variance (ANOVA)- after being logarithmically transformed- with factors for treatment, period, sequence and rabbit nested within sequence. Confidence limits were calculated on the basis of the least squares means and the mean square error obtained from the ANOVA. The test procedure for logarithmically transformed data is equivalent to requiring the 90% confidence limits of the geometric mean ratio, to lie within the strict bioequivalence confidence limits of 80-125 %.[24]

Results and discussion

The limit of detection (LOD) was as low as 2 ng/ml. While the limit of quantitation (LOQ) was found to be 6 ng/ml. For selectivity, analysis of plasma blank samples were tested for interference, and selectivity was assessed at the lower limit of quantification. Figure 1 shows a representative chromatogram of a plasma sample containing both ciprofloxacin and enrofloxacin. Plasma blank samples were prepared as described before except the addition of ciprofloxacin and enrofloxacin. Chromatograms of blank samples showed no interfering peaks at the retention times of ciprofloxacin and enrofloxacin peaks. A plasma blank chromatogram is shown in Figure 2.

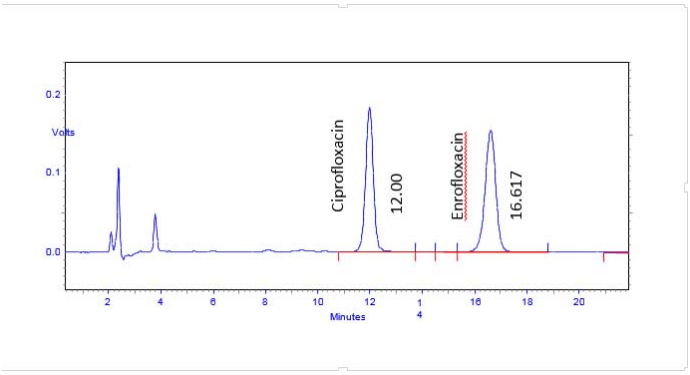

Figure (1): Chromatogram of Plasma sample containing ciprofloxacin 0.8 µg/ml (RT 12.0 min) and enrofloxacin 0.5 µg/ml (RT 16.6 min)

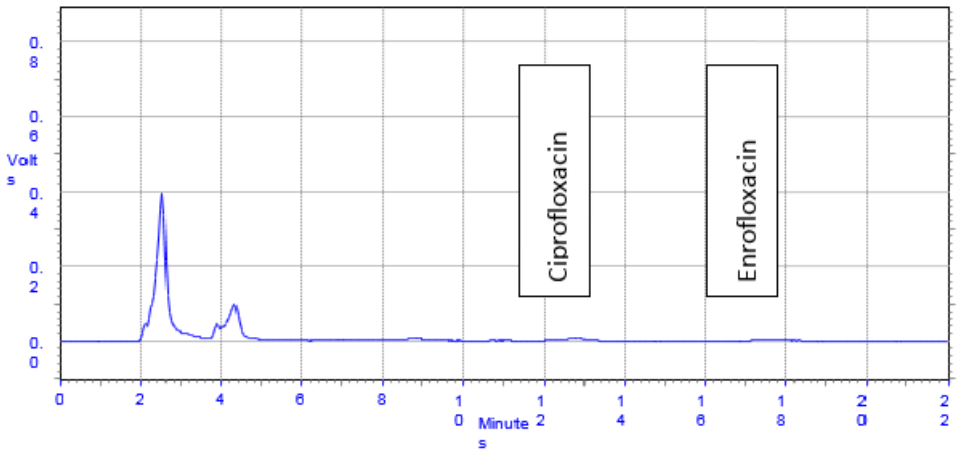

Figure (2): Plasma blank chromatogram

In order to evaluate any possible interactions between cabbage extract and either ciproflioxacin or enrofloxacin during HPLC analysis, cabbage extract was administered to two rabbits and plasma samples were collected at 30 and 60 minutes after administration. The results showed no peaks appearing at the retention times of both ciprofloxacin and enrofloxacin.

Standards for plasma ranging from 0.010-8 µg/ml were used to produce the standard curves. Calibration curves were constructed. The linearity was verified using least squares linear regression with a correlation coefficient (r) of at least 0.999. Multiple linear regression analysis showed no significant differences in either the slope or the intercept of four calibration curves. Accordingly, the average of the four calibration curves was used in calculating the plasma concentration of ciprofloxacin in the collected samples.

Within day variation (Intraday variability) was determined by assaying six standard plasma samples (0.01, 1, 3, 4, 6, and 8) five times each on the same day. Also, they were assayed at least 24 hrs apart, in different runs, to determine between day variation (interday variability). Results for the six concentrations chosen are summarized in Table (1).

Table (1)
Intra- and Interday coefficients of variation (CV) for the six concentrations in plasma

CIPROFLOXACIN CONCENTRATION(µg/ml)	INTRADAY CV %	INTERDAY CV %
0.1	4.23	4.84
0.4	0.87	0.89
3	1.74	1.85
4	0.27	2.92
6	0.72	0.92
8	3.53	3.59

Mean concentration time profiles are shown in Figure 3 and the obtained pharmacokinetic parameters for

rabbits and their means and standard deviations are summarized in Table 2. In the present study, ciprofloxacin was found to be rapidly and well absorbed in rabbits after oral administration. Pharmacokinetic parameters of ciprofloxacin in this study are in agreement with previous studies.[23,25,26,27]

Table (2)

Pharmacokinetic parameters for rabbits (control and test) and their means and standard deviations

Parameter	Control			test			
	mean	SD	CV%	Mean	SD	CV%	P value
T_{max} (hr)	1.40833	1.256476	89.217	0.753323	0.874008	116.020	0.1927
C_{max} (ng/ml)	1492.31	1408.343	94.373	2298.68	1952.736	84.950	0.3035
λ_Z (hr^{-1})	0.26863	0.135764	50.539	0.28804	0.177749	61.710	0.7869
$t_{1\backslash 2}$ (hr)	3.08653	1.249453	40.481	3.90547	3.118533	79.850	0.4508
AUC $_{0\rightarrow t}$ (ng.hr/ml)	6026.83	5526.342	91.696	7958.97	6565.602	82.493	0.4856
AUC $0\rightarrow \infty$ (ng.hr/ml)	7117.76	6628.768	93.130	11684.65	11479.48	98.244	0.2903

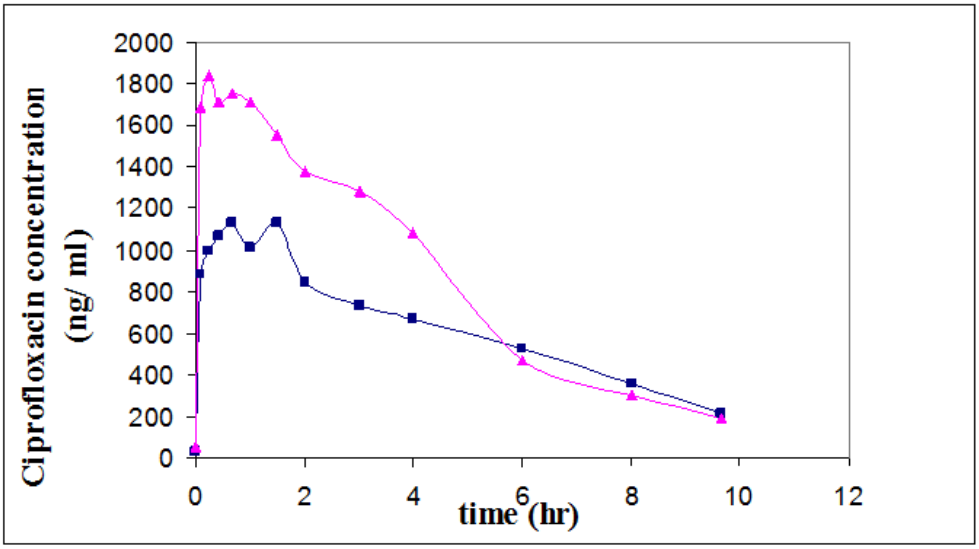

Figure (3): Mean concentration- time profiles of test (▲) and control (■)

Statistical analysis showed no significant effect for cabbage extract on the concentration-time profile for ciprofloxacin. The 90% confidence interval for the ratio of the two treatments for AUC (Logarithmically transformed AUC) was 51.75 - 213.78. When co-administered with the cabbage extract, T max for ciprofloxacin in plasma was reduced to the half; C max was increased by 1.5 times and AUC was 1.32 times higher.

The high variability in the obtained pharmacokinetic

parameters indicates the need for a larger sample size. However, the mean values for the concentrations suggest some potentiation for the cabbage extract on the produced ciprofloxacin concentration time profile. The partition coefficient for ciprofloxacin base was evaluated in this study to investigate the potential effect for cabbage extract on the absorption of ciprofloxacin.

Partition coefficient of ciprofloxacin base was determined using octanol: phosphate buffer (pH 7.4). Average partition coefficient of ciprofloxacin alone and in the presence of brassica was 0.19 and 0.25, respectively. However, when the pH of the buffer brassica phase was adjusted from 7.32 to 7.4, the partition coefficient was reduced to 0.19.

The effect of brassica extract on the solubility of ciprofloxacin was studied, by mixing ciprofloxacin base with phosphate buffer or with brassica extract alone and concentrations were measured. The procedure was repeated five times. The mean concentration in brassica extract (pH 7.32) was 3.68 mg/mL which was significantly higher than that in the buffer which was 3.25 mg/mL (p-value<0.001). The increase in solubility of ciprofloxacin in the presence of cabbage was due to pH (lower than the isoelectric point of ciprofloxacin (ciprofloxacin is found unprotonated). [28]

There are few previous studies that investigated the interaction between cabbage and drugs. A diet containing cabbage and sprout reduced the AUC of Acetaminophen by 16 % and that of oxazepam by 17%.[29] However in another study by Yamasaki, cabbage had no effect on the pharmacokinetics of acetaminophen.[30]

The increase in bioavailability of ciprofloxacin might be caused by the solubilization effect of the anionic glycosides (glucobrassicin) or brassicasterol (sterol ester) which could modulate the activity of membrane-bound enzymes. [31,32]

Conclusion

A validated HPLC method for the analysis of ciprofloxacin in rabbit plasma was used to study the potential effect for cabbage extract on ciprofloxacin absorption when co-administered to rabbits via oral route. Statistical analysis showed that when co-administered with cabbage, Tmax for ciprofloxacin in plasma was reduced to the half; Cmax was increased by 1.5 times and AUC was 1.32 times higher. Results suggest a potentiating effect of cabbage extract on ciprofloxacin absorption which might be due to the anionic glycosides and sterols found in cabbage.

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دراسة تأثير مستخلص الملفوف (Brassica oleracea) على الحركة الدوائية للسيبروفلوكساسين في نموذج حيواني

أماني سعادة[1]، وطلال أبو رجيع[1]، ونصر شريم[2] معتصم الغزاوي[1]

[1] كلية الصيدلة، الجامعة الأردنية، عمان، الأردن

[2] قسم الصيدلة، كلية الطب والعلوم الصحية، جامعة النجاح، نابلس، فلسطين.

ملخص

تم دراسة تأثير الملفوف *Brassica oleracea* على الحركية الدوائية للمضاد الحيوي واسع الانتشار السيبروفلوكساسين باستخدام الأرانب.

تم إعطاء الأرانب جرعة واحدة من السيبروفلوكساسين (40 ملغم/كغم) بشكل معلق، وفي نفس الوقت تم إعطاء الملفوف (2غم/ كغم) بشكل خلاصة مائية.

أجريت الدراسة على اثني عشر أرنبا، سحبت منها العينات على فترتين بترتيبين مختلفين، وبالتبادل، وبترك سبعة أيام بين الفترتين للتخلص من الدواء من أجسام الأرانب.

تم سحب عينات الدم بفترات (5، 15، 25، 40، 60، 90، 120، 180، 240، 360، 480، 580 دقيقة). وقد تم تحليلها باستخدام جهاز التفريق اللوني عالي الأداء (HPLC) باستخدام عمود سيليكا معكوس للتعرف على السيبروفلوكساسين وتحديد تركيزه في البلازما.

باستخدام هذه الطريقة والظروف المستخدمة، فإن أقل تركيز من دواء السيبروفلوكساسين تم تحديده كان 6 نانوغرام/ مل، والحد الأدنى للكشف عن وجود السيبروفلوكساسين كان 2 نانوغرام/ مل.

وقد كان المنحنى المعياري خطيا بتركيز 0.01–8 ميكروغرام /مل، وبمعاملات ارتباط > 0.999، وكان الانحراف المعياري النسبي خلال اليوم أو خلال الأيام لعينات الضبط أقل من 5%.

أظهرت الدراسة أنه عند إعطاء دواء السيبروفلوكساسين والملفوف في نفس الوقت فإن وقت الذروة للسيبروفلوكساسين في البلازما قد انخفض إلى النصف، بينما أظهر تركيز الذروة زيادة بمقدار مرة ونصف، بينما أبدى التركيز تحت المنحنى زيادة بمقدار 1.32 مرة.

أظهرت النتائج التي تم الحصول عليها أن هناك تأثيرا داعما ومقويا لنبات الملفوف لتأثير دواء السيبروفلوكساسين، والذي من الممكن أن يعزى لوجود بعض المواد الفعالة في الملفوف مثل الجليكوسيدات الكبريتية والستيرولات.

الكلمات الدالة: الملفوف Brassica Oleracea، كرنب، سيبروفلوكساسين، أرنب.

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