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The Effect of Interval Antacid Giving Time on Oral Bioavailability of Ciprofloxacin Using Rabbit Blood

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A B S T R A C T

Most people use drugs at the same time. This concomitant use is susceptible to interaction which results in reduced bioavailability of one of the drugs. Ciprofloxacin is often used to prevent gram-positive and negative bacterial infections. One of them is for gastrointestinal infections. This causes most of the use of ciprofloxacin often combined with antacids. Fluoroquinolone antibiotics, one of which is ciprofloxacin when given together with antacids, can cause chelate compound formation. This causes a reduced bioavailability of ciprofloxacin in the body. The purpose of this research is to look effect of the interval of antacids giving time on oral bioavailability of ciprofloxacin Analysis of ciprofloxacin levels in the blood was analyzed using a High Performance Liquid Chromatography (HPLC) apparatus. The results showed that there was a significant difference between the bioavailability of ciprofloxacin and the variation of the interval of administration with antacids, where at each interval of administration there were differences in pharmacokinetic parameters. The ciprofloxacin AUC showed the lowest value (101.1717 mcg / ml. Hour) when ciprofloxacin was interrogated for 120 minutes with antacid.

Keywords: ciprofloxacin, antacids, bioavailability, high performance liquid Chromatography

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INTRODUCTION

Drug interactions are interactions that occur between drugs consumed simultaneously. Drug interactions can produce good effects or bad effects, this is one of the causes of Drug Related Problems (DRPs) or unwanted events related to medication[1].Drug interaction is one of the factors that influence the body's response to treatment. Drug interactions are considered clinically important if they result in increasing toxicity and reducing the effectiveness of drugs that interact so that therapeutic effects change[2].

Antibiotics are one of the drugs that often experience interactions[3]. One drug that can interact with antibiotics is antacid drugs. Antacid drugs containing Aluminum and Magnesium can form chelates which can reduce the potential of ciprofloxacin. To avoid chelate formation, it needs to be given a period of administration[4].

Concentration-dependent antibiotics, such as aminoglycosides and florquinolones, show a significant increase in the value of microbial eradication if the level is increased by 4-64 times from the value of the minimum inhibitory concentration and high peak levels can be achieved by giving one infusion times, and infecting pathogenic microbes are rapidly eradicated. Conversely, antibiotics that is time-dependent, such as beta lactam, glycopeptides, macrolides, and clindamycin do not show a significant increase in bacterial eradication with an increase in antibiotic levels. The maximum bactericidal effect is obtained when the time above the minimum inhibitory concentration is at least 70% of the dose interval[5].

MATERIAL AND METHODS

Materials

Ciprofloxacin, Antacid, Methanol for HPLC, acetonitrile, formic acid, aquabides.

Apparatus

Measurement of blood ciprofloxacin concentration using the High Performance Liquid Chromatography Shimadzu LC-20AD apparatus.

Preparation Phosphoric Acid 0.025 M: Acetonitrile Solution

Add 0, 85 ml of 85% phosphoric acid to a 500 ml flask, then add 450 ml of aquabides and add pH to 3.0 with the addition of trietylamine and then fill it to the marked line. Made of a phosphoric acid mixture: acetonitrile (80: 20)[6].

Preparation Ciprofloxacin Lead Standard Solution

25 mg of ciprofloxacin, put into a 100 ml measuring flask, dissolved and diluted with aquabides until the marking line obtained a solution with a concentration of 250 mcg / ml. Then filtered, then the filtrate is used as a lead standard solution[7].

Preparation Ciprofloxacin Calibration Curves

Taken standardized solution of standard ciprofloxacin as much as 0.02, 0.2, 2, 5, 10, 15, 20 ml, each put into a 50 ml volumetric flask, diluted with the mobile phase of sign line, obtained a concentration of 0.1 1 , 10, 25, 50, 75 and 100 mcg / ml then each concentration was injected six times into the high performance liquid chromatography (HPLC) system with a volume of injection of 20 µl. Measured at a wavelength of 278 NM with a flow rate of 2 ml / minute, then recorded the area and height of the peak shown in the chromatogram and made a calibration curve and calculated the regression equation[7]

Preparation Suspension Ciprofloxacin

Sodium CMC 500 mg, then sprinkle above mortar who has been contains 20 ml of hot water. Let it stand for 15 minutes until sodium CMC expands. After expanding snorted sodium CMC, then take ciprofloxacin approximately 50 mg, scour to homogeneous. Then add it aquadest little by little to mass evenly mixed. Then add to 100 ml[7].

Manufacture Suspension Antacids

500 mg sodium CMC Na, then sprinkle above mortar who has contains 20 ml of hot water. Let it stand for 15 minutes until sodium CMC expands. After expanding snorted sodium CMC, then put in antacids as much as 50 mg, scour to homogeneous. Then add it aquadest little by little to mass evenly mixed. Then add to 100 ml[7].

Blood Sampling

Take blood, rabbit male more 15 ml less than the marginal vein of the ear rabbit, inserted into the tube already contains 2 drops of heparin. Prepare 7 piece tube and each tube entered Solution Ciprofloxacin Standard with concentration: 0.1 mcg/ml, 1 mcg/ml, 10 mcg/ml, 25 mcg/ml, 50 mcg/ml, 75 mcg/ml, and 100 mcg/ml[8].

Determination Ciprofloxacin In Plasma Using High Performance Liquid Chromatography

Each rabbit has been grouped into six:

1. Only ciprofloxacin is given.
2. Given ciprofloxacin and antacids together.
3. Given antacids and ciprofloxacin at 30 minute intervals.
4. Given antacids and ciprofloxacin at intervals of 60 minutes.
5. Given antacids with ciprofloxacin at intervals of 90 minutes.
6. Were given antacids with ciprofloxacin at intervals of 120 minutes.

Take blood, rabbit each 1 ml of the marginal vein of the ear rabbit and entered into the tube already contains 2 drops of heparin. Centrifuged for 5 minutes with speed of 4000 RPM. Pipette 0.5 ml of plasma, inserted to in politube and 0.5 ml of acetonitrile was added to precipitate protein then divorced. Centrifuged with speed of 4000 RPM for 5 minutes. Separated supernatant from sediment and used as blank.

Then animal test given solution ciprofloxacin with dose has been converted (dose) human to dose rabbit against dose prevalent. Each rabbit taken his blood approximately 1 ml of vein marginal ear rabbit with range time that has been set. Range the time ranges: 30, 60, 90, 150, 210, 270, 360, 450, and 540, 660 and 780 minutes Centrifuged for 5 minutes with speed of 4000 revolutions per minute. Separated supernatant from sediment. Pipette 0.5 ml of plasma, inserted to in politube and 0.5 ml of acetonitrile was added to precipitate protein then divorced. Centrifuged with a speed of 4000 RPM for 5 minutes. Separated supernatant from sediment, then be measured with an HPLC apparatus with injecting it as much as 20 µl.

Figure 1: High Performance Liquid Chromatography Apparatus

RESULTS AND DISCUSSION

From the experiment, the standard measurement results can be seen in the Table 1 and Figure 2.

Table 1: The Results of the Standard Analysis of Ciprofloxacin Using Rabbit Blood

S. No	Concentration (mcg / ml)	Area
11	0.1	7212
22	1	42613
33	10	182830
44	25	381587
55	50	768858
66	75	1126419
77	100	1544233

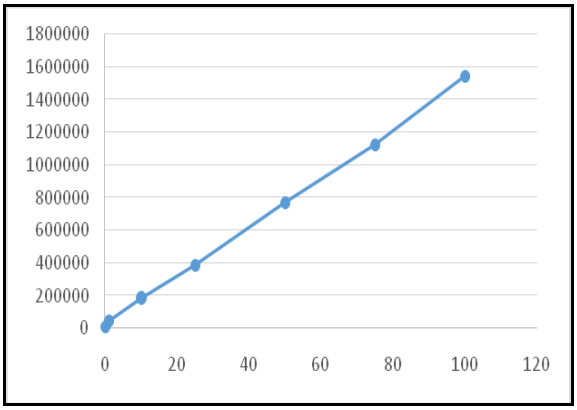

Figure 2: Ciprofloxacin Standard Curve

Standard linearity curve is obtained as follows, with the value r = 0.9996 and the regression equation Y = 15979.55159 X - 1288.88268.

From the results of research conducted it can be concluded that interval administration of ciprofloxacin with antacids affects the bioavailability of ciprofloxacin. from the results of the research conducted, the AUC, AUMC, MRT, Ka, Kel, half-life, C max, and ciprofloxacin T max values were greater than of ciprofloxacin in combination with antacid. Differences in Pharmacokinetic parameters could seen on Table 2

Table 2: Differences In Pharmacokinetic Parameters Ciprofloxacin With different intervals with Antacids

Parameters	Control	0 Minute	30 Minutes	60 Minutes	90 Minutes	120 Minutes
AUC (mcg/ml.hour)	221,586667	219,911667	189,67	159,693333	131,71	101,1717
AUMC	1549,11167	1532,19333	1309,74833	1082,43667	868,191667	652,76
MRT (hour)	6,99166667	6,96666667	6,905	6,77833333	6,59333333	6,451667
Ka ($hour^{-1}$)	1,02824138	1,00379851	1,13436811	1,19912951	1,15764942	1,293514
Kel ($hour^{-1}$)	0,17016667	0,1705	0,17183333	0,17633333	0,18233333	0,189
$T_{1/2\ el}$ (hour)	4,07433333	4,065	4,03383333	3,92916667	3,80166667	3,6675
Cmax (mcg/ml)	26,5516667	26,2916667	23,4883333	20,4433333	17,1266667	13,92333
Tmax (hour)	2,375	2,355	2,32833333	2,28166667	2,27833333	2,256667

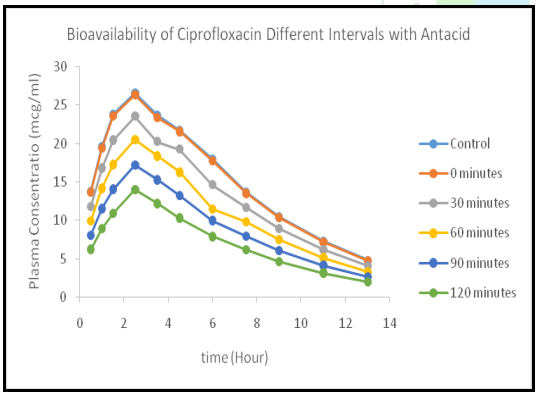

Figure 3: Log Concentration Vs Time

From the graph 2 above it can be seen that there are differences in chart position and graph value. This suggests that under antacid administration can reduce the bioavailability of ciprofloxacin

CONCLUSION

The use of antacids and ciprofloxacin together is not recommended, because it can cause poor bioavailability of the ciprofloxacin drug. Antacid drugs containing Aluminum and Magnesium can form chelates which can reduce the potency of ciprofloxacin. The potency of ciprofloxacin which is an antibiotic depends on concentration will decrease if combined with antacids. This can cause bacterial resistance problems. Avoid using antacids together with ciprofloxacin.

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