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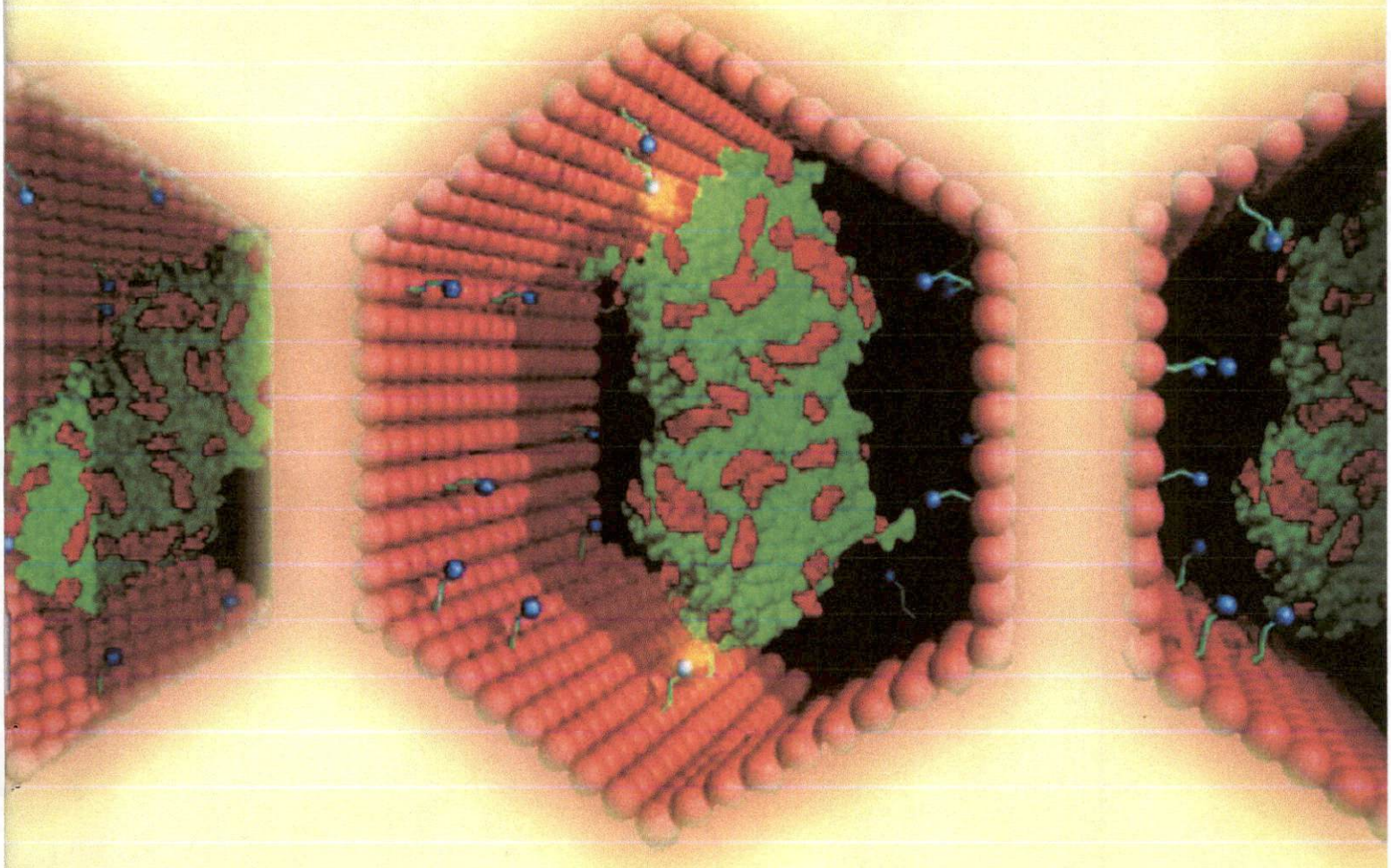

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DAFTAR ISI

Gambar sampul:
Skema amobilisasi molekul enzim didalam pendukung nanoporous. *Credit: Eric Ackerman, PNNL.* Gambar didownload dari : http://nanotechweb.org/

Efect of $Al(OH)_3$ and $Mg(OH)_2$ Suspesion Dosage Form on the Absorption of Oral Ciprofloxacin

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Potential interaction of fluroquinolone with other drugs have been established in the several reports. The absorption of fluroquinolones were almost entirely inhibited by concomitant administration of di and trivalent cations such magnesium and aluminium in the antacids were significantly decreased the absorption of ciprofloxacin through formation of a complex. The effect of antacid (Antasida DOEN) 1.4 ml/kg body weight doses which containing polyvalent cation $Mg(OH)_2$ and $Al(OH)_3$ on the absorption of ciprofloxacin. were examed in healthy rabbit. Twelve subjects were given 23 mg/ml BW ciprofloxacin alone as control. On day 8 the six subjects were given antacid and ciprofloxacin concomitant and the other were given antacid two hours after ciprofloxacin. The absorption parameters of ciprofloxacin were determined by spectrofluorometric method. Those parameters were Cmax, tmax and AUC, the administration of ciprofloxacin and antacids concomitantly result Cmax, tmax and AUC were 1.27±0.45g/ml; 110±48.99 minutes and 248.63±94.77g.minutes/ml respectively in a significant decrease in ciprofloxacin absorption ($p<0.05$) and the administration of antacids two hours after ciprofloxacin result Cmax, tmax and AUC were 1.37±0.65g/ml;75±36.74 minutes and 245.09±100.46 g.minutes/ml respectively in a significant decrease in ciprofloxacin absorption ($p<0.05$). Percentages of relative bioavailability compared with control values were 27.06±16.70% and 8.77±6.97% for concomitant and two hours after ciprofloxacin respectively.

Keywords: *Ciprofloxacin, $Mg(OH)_2$, $Al(OH)_3$, antacid, Spectrofluorometric*

INTRODUCTION

Ciprofloxacin (fig.1) is fluoroquinolone antibiotic a broadspectrum which can against positive and negative microorganism as synthetic antibiotic and bactericid especially negative microorganism P. aeruginosa (Mc Evoy, 2002). Ciprofloxacin were used for treatment desease: GIT, respiratory tract up and down; urinary tract, skin infection, which inhibit enzim topoisomerase II sub unit A (ADN gyrase) and topoisomerase IV in DNA synthesis as a potential antibacterial (Ball, 2000). Plasma concentrations in healthy volunteers reach a mean peak drug plasma concentrations (C_{max}) of approximately 2.8 and 5.2mg/L within 1 to 2 hours after oral administration of ciprofloxacin 250 and 500mg tablets, respectively. The oral absorption is very rapid and complete, the bioavailability of oral ciprofloxacin approaches 100% and it little affected by administration with food (Fish and Chow, 1997).

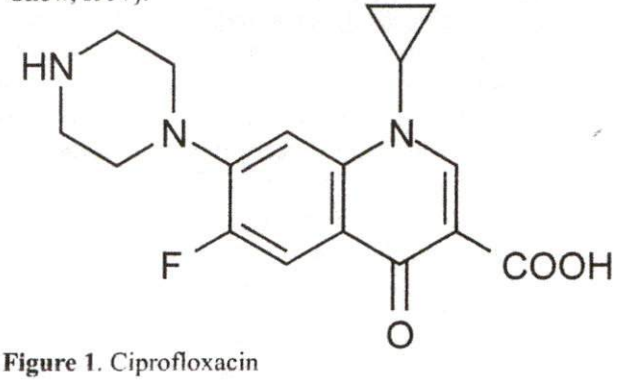

Figure 1. Ciprofloxacin

In separate study, the effect of antacid, sucralfat; food, H_2 receptor antagonis on fluoroquinolon interaction was examined (Radanst *et al.*, 1992). The interactions with aluminum and magnesium containing antacid with fluoroquinolones as ciprofloxacin, resulting in significantly decrease absorption and bioavailability when administered concurrently (Stockley, 2001). Nix *et al.* (1989) were reseached that plasma concentrations in healthy volunteers decreased 85% when ciprofloxacine was gived 5 until 10 minute after antacid (Maalox®) because ciprofloxacine and antacid formed complex metal (Stockley, 2001). A measure such as t_{max} does not adequately describe situations in which double peaking may occur or which prolonged absorption are observed. Antacid ($Mg(OH)_2$ and $Al(OH)_3$) is widely used for a variety of indications (duodenal ulcer disease, dyspepsia, saur stomach), the mechanism of antacid are neutralize acid and stimulate mucosal defenses (Mc Evoy,2002). The probably that ciprofloxacin will be given to patients receiving long term therapy with antacid/H_2 blocker is high. Since antacid affect oral absorption of variety of agents, the effect of administration of antacid on the absorption of ciprofloxacin was studied (Radanst *et al.*, 1992), Therefore studies were perform to determined the effect of antacid administration on the oral absorption of ciprofloxacin in healthy rabbits by spectrofluorometric (El-Kommos *et al.*, 2003)

MATERIAL AND METHODS

Materials and reagents. Ciprofloxacin was a kind gift of PT Kimia Farma. Methanol (HPLC gradient) was purchased from JT Baker, antacid DOEN was a kind gift of First Medipharma, dipotassium hydrogenphosphate and phosphoric acid 85% were purchased from Merck (Darmstadt, Germany), double distilled water was obtained from PT. Ikapharmindo Putramas (Indonesia).

Heparin 500unit/ml, ammonium molybdat were purchased from Fluka AG, citric acid was purchased from Riedel-de Häen, xylol was obtained from Brataco Chemika, Acetonitril was purchased from Riedel-de Häen,

Apparatus. Hitachi F-4000 Spectrofluorometer (Japan) was used for fluorometric measurements, Direct Reading Micro Balance LM-20 Libror, Ultrasonic Cleaner Sakura US-10E, Centrifuge Hettich, Protofix 32, Thermolyne Barnstead type 37600, glassware and injection syringe.

Standard preparations. Stock solutions containing 1g/ml of each ciprofloxacin was prepared in methanol. Working standard solutions containing 100-600ng/ml was prepared by suitable dilution of the stock solutions with methanol.

Sampling. The method animal was used Australian Rabbit from Batu Malang, weight 2,5kg. Treatment antacid 14mg/kg BW of rabbit, 70mg/ml oral solution form and ciprofloxacin 23mg/ml kg BW of rabbits (Paget, 1964). The twelve rabbits were fast overnight before drug administration and 2 hours after the dose was administered. Water was allowed *ad libitum* 10 ml. Blood sample (2ml) were collected with injection syringe 2.5cc containing anticoagulant via ear of marginal venous. Samples were collecting in a vacuum test tube. Blood samples were obtained immediately before and 5, 10, 20, 30 ,45, 60, 75, 90, 120, 300 minutes after ingestion of the orally administered formulation.. Plasma was harvested and samples were stored at -20°C until assayed. Plasma concentration of ciprofloxacin were determined by spectrofluorometric. The assay was liniar over the calibration range 100 to 600ng/ml (El-Kommos *et all*, 2003)

General procedure. One milliliter aliquot volumes of standard or sample solutions were transferred into 10-ml calibrated flask. One milliliter of the ammonium molybdenum solution (7.5g/ml) was added and pH was adjusted to 3.5 using 1 ml of Teorell and Stenhagen buffer solution. The volume was completed with methanol. The relative fluorescence intensity of resulting solutions were measured against reagent blanks treated similarly at the excitation and emission maxima specified for ciprofloxacin. (El-Kommos *et al.*, 2003).

Plasma treatment (El-Kommos *et.al.*, 2003). Five milliliter of plasma were deproteinized by the addition of 10 ml acetonitrile, centrifuged at 4000 rpm for 5 minutes. One milliliter of clear supernatant was spiked with 1 ml of drug stock solution. The mixture was then extracted with 2 portions; each of 5ml chloroform. The chloroform extract was collected, evaporated on a boiling water bath, then appropriate dilutions were made to obtain drug solutions containing 100, 300 and 500ng/ml, then general procedure was followed.

The effect of antacid. The twelve rabbits were the same treatment as ciprofloxacin alone, and the day 8, six rabbits were administered antacid and ciprofloxacin concomitant and the other one were administered antacid 2 hours after ciprofloxacin.

The pharmacokinetic analysis of plasma concentration of ciprofloxacin were determined using spectrofluoro metric method . The assay had a dynamic range of 10 to 60 ng/ml (El-Kommos *et al.*, 2003). The maximum plasma concentration of ciprofloxacin (C_{max}) and earliest time at which C_{max} occurred (t_{max}) were estimated directly from the experimental data. The intensity under the plasma concentration-time curve from time zero to the last time (t) plasma ciprofloxacin was measurable (AUC_{0-300}) was estimated by the linier trapezoidal approximation (Shargel, 2005).

Student's t tests with 95% confidence limits were used to examine pair-wise differences between the groups. Value of $p<0.05$ were considered to be statistically significant (Santosa *et al.*, 2005).

Previous studies have demonstrated that the absorption of orally administered ciprofloxacin is impaired by concomitant administration of magnesium and aluminum-containing antacids. This interaction may result from the formation of ciprofloxacin – metal complexes that poorly absorbed (Nix *et al.*, 1989). The mean plasma ciprofloxacin concentration-time curves for the administered antacid and ciprofloxacin concomitant groups were significant different ($p<0.05$). Cmax, tmax and AUC were 1.27±0.45µg/ml; 110±48.99 minutes and 248.63±94.77µg. minutes/ml respectively (figure 2, and Table 1 as T1) and the administered antacid two hours after ciprofloxacin result Cmax, tmax and AUC were 1.37 ±0.65µg/ml; 75±36.74 minutes and 245.09±100.46µg. minutes/ml respectively in a significant decreased in ciprofloxacin absorption ($p<0.05$). Percentages of relative bioavailability compared with control values were 27.06± 16.70% and 8.77±6.97% for concomitant and antacid two hours after ciprofloxacin respectively.(Figure 3, and Table 2)

Table 1. Summary of pharmacokinetic parameter of the administrated antacid and ciprofloxacin concomitant (T1) and antacid 2 hours after ciprofloxacin (T2)

Variabel	Control T1 and T2	Treatment I and Treatment 2		
AUC 0-300minutts (µg.minute/L)	248.63±94.77	245.09±100.46	188.23±99.83	224.35±93.92
t max (minute)	110±48.99	75.00±36.74	170.00±72.66	65.00±12.25
C max (µg/L)	1.27±0.45	1.37±0.65	1.05±0.40	1.41±0.55

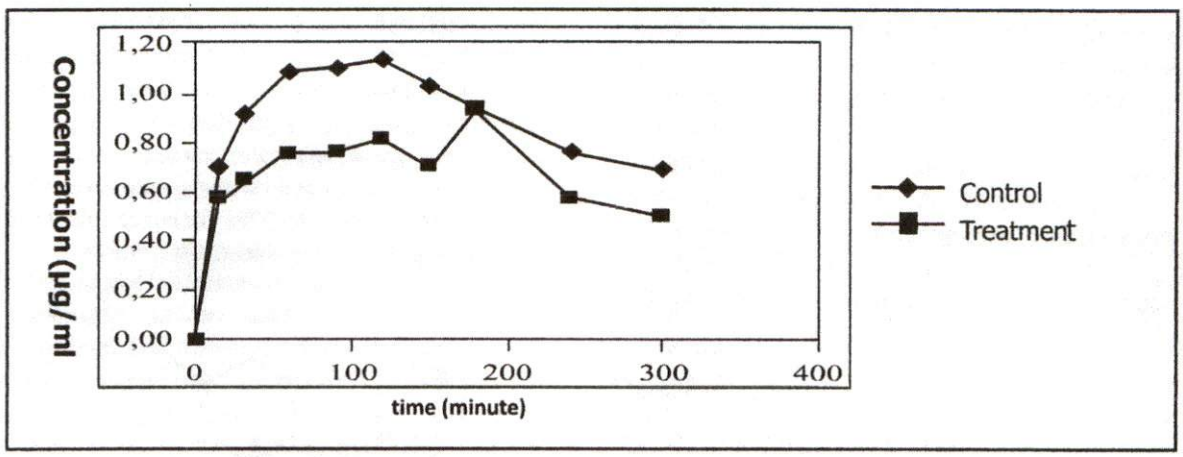

Figure 2. Concentration (µg/ml) versus time (minutes) curve from antacid and ciprofloxacin concomitant

Table 2. Summary of t account; t table and probability of absorption parameter

Absorption parameter	t account	t table	probability
Cmax Ti	1.468	2.571	0.202
T2	-0.283	2.571	0.788
AUC0-300			
T1	5.140	2.571	0.004
T2	3.313	2.571	0.021
T max			
T1	-1.581	2.571	0.175
T2	0.598	2.571	0.576

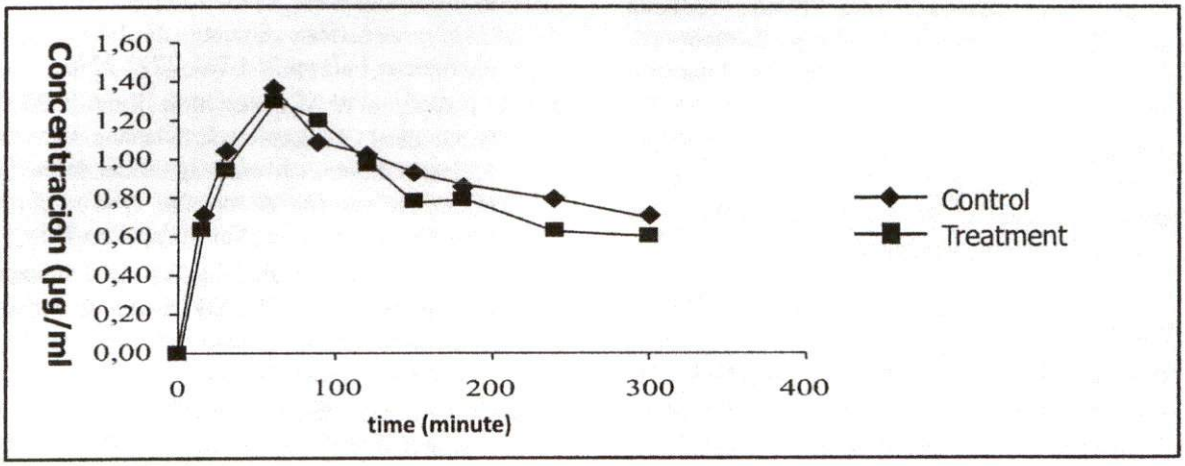

Figure 2. Concentration (µg/ml) versus time (minutes) curve administered antacid 2 hours after ciprofloxacin

RESULTS AND DISCUSSION

To determine the effect of timing on absorption of antacid and ciprofloxacin administered of single 23mg/kg BW dose of ciprofloxacin to 12 healthy rabbits in two-way crossover study, ciprofloxacin was given alone or combined with other an magnesium/aluminum containing antacid 14ml/kg BW; the timing of antacid and ciprofloxacin administration was varied (concominant and antacid 2 hours after ciprofloxacin). The literature describing reduced absorption of fluoroquinolones due to antacid administration to patients and volunteers is most extensive for ciprofloxacin (Figure 4) where in the gastro intestinal region the complex chelat form of antacid (metal = Mg and Al) and ciprofloxacin couldn't absorbed (Nix *et al.*, 1989; Brighty *et al.*, 2000) Those parameters were Cmax, tmax and AUC, the administration of ciprofloxacin and antacids concomitantly result Cmax, tmax and AUC $_{0\text{-}300}$ were 1.27±0.45 g/ml; 110±48.99 minutes and 248.63 ±94.77 g.minutes/ml respectively 55.29%, 53.91% significant different ($p<0.05$) (Santosa, *et al.*, 2005) respectively and t_{max} increased 180% but not significant different ($p>0.05$) (Table 1 and figure 2).

administration of the antacid 2 hours after ciprofloxacin decrease but not significant different in C_{max} 5.74% and AUC_{∞} 0.07% ($p>0.05$) respectively and t_{max} increased 8.77% but not significant different ($p>0.05$). The inhibition of absorption can be significant and potentially lead to the failure of the treatment, even when ciprofloxacin dose are separated from antacid dose by more than 2 hours (Radanst *et al.* 1992) in a significant decrease in ciprofloxacin absorption ($p<0.05$) and the administration of antacids two hours after ciprofloxacin result Cmax, tmax and AUC were 1.37±0.65g/ml; 75±36.74 minutes and 245.09±100.46 g.minutes/ml respectively in a significant decrease in ciprofloxacin absorption ($p<0.05$). Percentages of relative bioavailability compared with control values were 27.06±16.70% and 8.77±6.97% for concomitant and two hours after ciprofloxacin respectively.

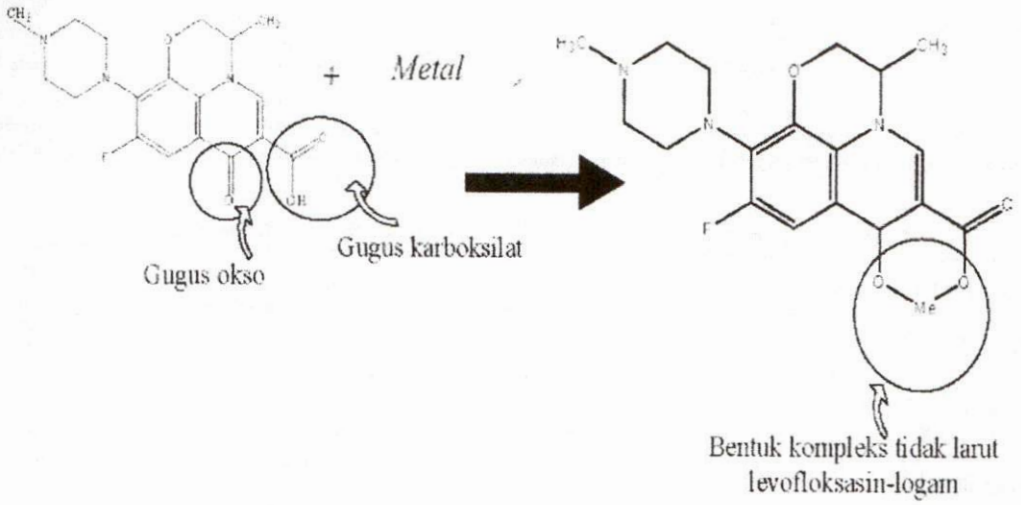

Figure 4. Ciprofloxacin/ levofloxacin and metal complex form the reaction (Nix *et al.*, 1989; Brighty *et al* , 2000)

Conclusions. Complex form of ciprofloxacin with $Mg(OH)_2$ and $Al(OH)_3$ re-precipitated in small intestine would play an important role in the reduced bioavailability (C max and AUC) if ciprofloxacin co-administration with Mg and Al–containing antacids concomitant.

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