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The Effect of Ranitidine Against Pharmacokinetics profile of Diclofenac Sodium

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Abstract : Ranitidine is one of the *H2-antagonist* which potent to inhibit the metabolism of other drugs by inhibits enzyme activity of metabolism inhibitor by binding the cytochrome P-450 that are reversible in forming complexes, so that the active of cytochrome P-450 will decrease. In many cases of ranitidine diseases ranitidine is widely used as a combination therapy with other drugs one of them is diclofenac sodium. Diclofenac sodium metabolism is occurs in the hearts and involving cytochrome P-450. This combination can lead into interaction on pharmacokinetic phase, especially in metabolism and excretion phase of diclofenac sodium. The objective of this research was to determine the effect of ranitidine on the pharmacokinetics profile of diclofenac sodium, especially in metabolism and excretion phases.

The method used in this research is experimental methods using 27 male white rats galur wistar (*Rattus Norvegicus*). These rats were divided into 3 groups. First treatment group was given by diclofenac sodium solution, second treatment group was given by diclofenac sodium and then ranitidine for seven days with consecutively and for third treatment group was given by diclofenac sodium and ranitidine withsimultaneously. Diclofenac sodium dose is 4.5 mg / kg and ranitidine dose is 13.5 mg / kg for each group. The measurement of drug levels in plasma diclofenac sodium was carried out by using High Performance Liquid Chromatography (HPLC). The resultwas analyzed by using one-way ANOVA.

The results showed that no pharmacokinetic parameter values in the absorption phase did not show any significant effect on each group. While the phase of metabolism and excretion showed significant difference between control group with the other two treatment groups, but between the other two treatment groups did not showed any significant differences.

Keywords: pharmacokinetics, metabolism inhibitor, diclofenac sodium, ranitidine.

Introduction

One of drug interactions mechanisms that occur in the body is pharmacokinetic interactions that affect the absorption, distribution and elimination (metabolism and excretion) of other drugs, it means drug levels would be increased or decreased [1.] Metabolic interaction processes are the most cases that occurred, whereabout 50- 60% of drugs that used in treatment can interact each others at the same enzyme [2.]

Diclofenac sodium is a simple derivative of phenyl acetate including *Non-Steroidal Anti-Inflammatory Drug* (NSAID) of the strongest anti-inflammation and recommended for chronic inflammatory conditions such as rheumatoid arthritis, osteoarthritis, treatment of acute skeletal muscle pain and post surgery analgesia [3.4.]. Diclofenac sodium was experiencing *first past metabolism* that only 50% of drug will reach systemic circulation. Diclofenac sodium absorption through the gastrointestinal tract is rapid and complete. These drugs are binding 99% to plasma proteins with half-life around 1-2 hours [5.] Diclofenac Sodium have 4 pKa,

where practically insoluble in acidic solutions, but soluble in intestine fluid [6] . So the oral absorption of the diclofenac is not affected by gastric pH[7].

Diclofenac and ranitidine in many clinical conditions perhaps could be given in a long period. Pathophysiology of gastro reflux disease esophageal involved a pharmacological treatment as an option for antisecretory management therapy with histamine H2 receptor antagonists(cimetidine and ranitidine) [8].NSAIDs are metabolized by CYP2C9 substrate and presence of ranitidine may inhibit the metabolism at the same isozyme [9].

Earlier research said that there are very few drug interactions between diclofenac and ranitidine [7]. In the other research mentioned thatthe given of ranitidine previously didn't affected the treatment and also did not have significant influence on the parameters of diclofenac sodium [9.10]. Pharmacokinetic parameters in those researches just only used in absorption phase.

In this research, evaluation and testing phases of whole pharmacokinetics will be done, especially to determine the effect of ranitidine on metabolism phase and sodium diclofenac excretion.

Materials and Methods

Equipments

The equipment used in this research were: HPLC unit (Shimadzu), Sonicator (Branson 1510), politube, *beaker glass , vortex, water bath, centrifuge,* flask, pH meter, measuring cups, analytical balance (Baeco Germany), pipette volume, pipette, gloves, syringes (Terumo), oral sonde, stopwatch, rat cage, masks, animal scales and other tools.

Material

Materials used in this research were: diclofenac sodium (Kimia Farma TBK), ranitidine (Peddadevulapalli), ibuprofen (Granules-Biocause Hubei Pharmaceutical CO. LTD), sodium CMC, methanol (E.Merck), sodium acetate, Hydrochloric acid concentrated (E.Merck), ethanol 70%, 0.5 µm PTFE membrane filter, TCA, heparin (PT. Pratapa Nirmala), distilled water, (PT. Ikapharmindo Putramas).

Experimental animals

The experimental animals used in this research are male rats galur Wistar (*Rattus Norvegicus*) weighing ± 200 g. The experimental animals were housed in standard cages with same condition, diet and under controlled conditions. Acclimatization of the experimental animals was conducted for seven days in order to be accustomed with the experimental condition.

Testing Against Pharmacokinetics Profile

In first treatment group, rats test were given by diclofenac sodium suspension at 4.5 mg /kg for doses. Each blood animal had taken from a vein of tail rats with a time interval is 0 hours; 0.25 hours; 0.5 hours; 0.75 hours; 1.25 hours; 1.75 hours; 2.25 hours; 3.25 hours; 4.25 hours; 6.25 hours; 8.25 hours. Blood taken incorporated into polytube that has been given heparin previously, then vortex and centrifuged at 3000 rpm for 10 min, take the supernatant and added by TCA 20% of 1 ml then vortex and centrifuged supernatant back and retrieved. After that, the levels will measureby using HPLC (High Performance Liquid Chromatography) with inject as much as 20 µl. In second treatment group, rats were given by ranitidine at 13.5 mg/kg for doses in advance for seven days consecutively. On the seventh day after ranitidine suspension was given, 4 hours later added diclofenac sodium suspension. Each animal's blood is taken similar like first group treatment. In third treatment group,rats were given by diclofenac sodium suspension and ranitidine simultaneously. Each animal's blood is taken similar like in first group treatment.

Data analysis of the research had done by using SPSS 17 with one-way ANOVA and Scheffe test.

Results and Discussion

Based on plasma injection in HPLC, data obtained from each treatment group includesdiclofenac sodium, diclofenac sodium after ranitidine giving for 7 consecutive days and diclofenac sodium with ranitidine simultaneously, can be seen in the average value of mean levels ± SD as shown in Table 1.

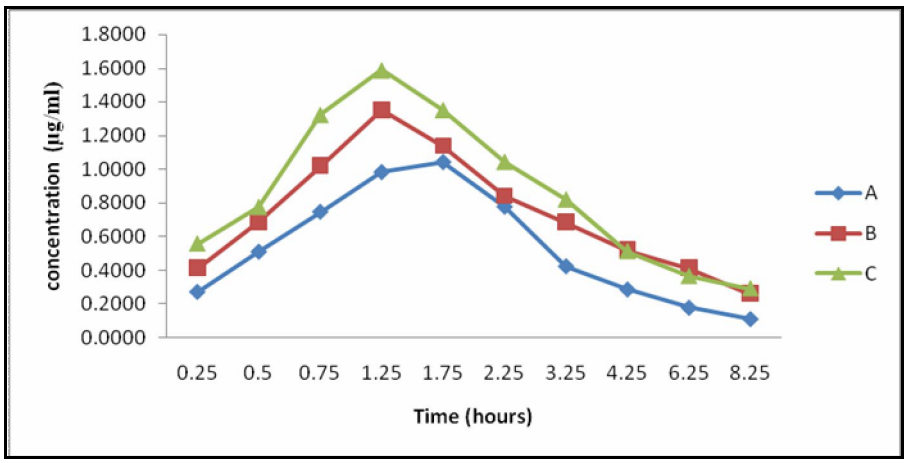
Table 1. Average Values Concentration of Diclofenac Sodium ± SDin Plasma

Time (Hours)	A (µg/ml)	B (µg/ml)	C (µg/ml)
0,25	0,2718±0,0207	0,4153±0,0698	0,5589±0,0207
0,5	0,5102±0,0649	0,6875±0,0796	0,7764±0,0649
0,75	0,7469±0,0819	1,0220±0,0981	1,3241±0,0819
1,25	0,9827±0,0660	1,3541±0,1835	1,5897±0,1144
1,75	1,0418±0,0835	1,1440±0,2105	1,3531±0,2533
2,25	0,7769±0,0711	0,8412±0,1250	1,0446±0,1205
3,25	0,4235±0,0918	0,6853±0,1454	0,8215±0,1240
4,25	0,2860±0,0648	0,5216±0,1457	0,5137±0,0820
6,25	0,1773±0,0540	0,4130±0,1290	0,3651±0,0665
8,25	0,1102±0,0245	0,2604±0,1031	0,2920±0,0243

Notes:

A: diclofenac sodium group
B: diclofenac sodium after ranitidine giving for seven days consecutively
C: diclofenac sodium with ranitidine simultaneously

Based on the average data concentration in plasma, can be seen in a curve, shown in picture 2 below.



Picture 2. The average value level of time for each treatment group

The result shown in table 1 used to determine the pharmacokinetic parameters of diclofenac sodium for each treatment group as shown in table 2

Table 2. Pharmacokinetics Parameter Value Diclofenac Sodium

Parameters	Treatment			Conclusion
	A	B	C	
lag time (jam)	0,236 ± 0,038	0,188 ± 0,049	0,201 ± 0,018	On B-C and A-C no significant differences
		0,752		
		0,168		
ka (jam-1)	2,364 ± 0,459	3,125 ± 1,259	3,333 ± 0,748	On A-B-C no significant differences
		0,088		
t1/2a (hours)	0,304 ± 0,067	0,260 ± 0,117	0,218 ± 0,049	On A-B-C no significant differences
		0,107		
Cmaks (µg/L)	0,890 ± 0,132	1,086 ± 0,114	1,354 ± 0,021	On A-B-C differences
Tmaks (jam)	1,252 ± 0,089	1,221 ± 0,167	1,116 ± 0,105	On A-B-C no significant differences
		0,088		
AUC 0-∞ (µg/L.jam)	3,747 ± 0,588	6,398 ± 1,487	6,786 ± 0,223	On B-C no significant differences
			0,682	
AUMC 0-∞ (µg/ml.jam2)	13,338 ± 3,036	34,582 ± 15,344	31,272 ± 2,384	On B-C no significant differences
			0,747	
MRT (jam)	3,529 ± 0,301	5,200 ± 1,229	4,607 ± 0,260	On B-C no significant differences
			0,260	
Kel (hour-1)	0,346 ± 0,038	0,234 ± 0,076	0,253 ± 0,015	On B-C no significant differences
			0,719	
t1/2el (Hour)	2,026±0,213	3,216±0,890	2,751±0,116	On B-C no significant differences
			0,206	
Vd (L)	889,565 ±38,54	774,466 ±167,48	633,263 ±35,27	On A-B no significant differences
	0,074			
CL (L/hour)	252,681±18,903	153,906±34,952	137,639±6,408	On B-C no significant differences
			0,348	

based on Table 2 can be seen the difference of the three treatment groups of test animals, but the difference in each parameter does not look significant, especially in the phase of absorption. Similar with Alioth Research., (1993) the value of the lag time, tmax da n t1 / 2 did not different significantly. C max values are the differences between the three treatment groups, while the value of AUC, MRT and different significantly in A group treatment with other treatments treatment but for treatment in B group and C was not significant difference. Inhibition of the enzyme causing the drug (substrate) lacking/not metabolized that is clearance metabolism (total clearance) is reduced, resulting in increased drug level in the blood. The increase of drug levels in the blood will be greater if small volumes of drug distribution [2.]

Clearance is a parameter that indicates the cleansing of diclofenac sodium from the body has decreased from the control treatment group as well as with elimination speed (Kel) while the elimination half-life increased compared to the control group. Elimination time half-life and area under the curve rise, while the clearance total and distribution volume decrease when compared to the treatment of the control, treatment of cimetidine in seven days in a row [11.] Metabolism of diclofenac in humans is mediated by CYP2C9 and if inhibited it will change the significant drug levels, because this enzyme plays a major role against drug metabolism. The metabolism of a drug through this pathway has been shown to be inhibited by cimetidine and ranitidine [2.9.]

Conclusion

Giving ranitidine may inhibit the enzyme metabolism of diclofenac sodium but does not significantly affect the parameters of pharmacokinetics in absorption Phase while in the phase of excretion is significant influence and others treatment of diclofenac sodium and ranitidine giving previously for seven consecutive days when compared to other group treatment of sodium diclofenac and ranitidine giving with simultaneously showed no significant effect on the pharmacokinetic parameters of diclofenac sodium.

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