



## Interaction Toxicity Study between P-glycoprotein Inhibitor (Captopril) and Inducer (Spironolactone) with Their Substrate (Lovastatin) in Male Rats

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### A B S T R A C T

An interaction toxicity study was performed to evaluate and compare the effect of P-glycoprotein (P-gp) inhibitor (captopril) and inducer (spironolactone) on their common substrate (lovastatin) that were done by comparing LD<sub>50</sub> of the acute study with their chronic form then with those combined therapeutic doses administered for 90 days. Therefore, isobolographic analysis and chronicity index were used as the parameters for this study. Forty rats were allocated into five groups according to the used treatment into: captopril, spironolactone, lovastatin, captopril + lovastatin and spironolactone + lovastatin using up and down method to determine their acute exposure LD<sub>50</sub> while ninety rats were used to perform the chronic stage of the study divided equally into six groups according to daily dosing regimen as following G1- control group administered distilled water orally; G2 administered captopril 0.7 mg/kg BW orally; G3-administered spironolactone 1.4 mg/kg BW orally; G4- administered lovastatin 0.57 mg/kg BW orally; G5-administered spironolactone 1.4 mg/kg BW orally and lovastatin 0.57 mg/kg BW, G6- administered captopril 0.7 mg/kg BW and lovastatin 0.57 mg/kg BW orally. The results of isobolographic analysis showed that the sort of interaction between P-gp inhibitor (captopril) and lovastatin alone and as combined administration showed to be antagonistic after acute administration while it was synergistic after chronic administration; for P-gp inducer, spironolactone and lovastatin were additive after acute administration and antagonistic after chronic administration. Chronicity index results showed that both captopril and lovastatin accumulated after administered each alone and showed more accumulation after their combined administration while the chronicity index for P-gp inducer (spironolactone) and lovastatin showed less total concentration in the body burden after their combined administration than alone one. In conclusion, it seems that P-gp inhibitor (captopril) causes accumulation of itself and substrate (lovastatin), while P-gp inducer (spironolactone) causes reduction on the body burden of itself as well as lovastatin possibly due to their effects on the kinetics of the body and this may affect the efficacy and safety of drugs.

**Keywords:** p-glycoprotein, inducer, inhibitor, substrate, LD<sub>50</sub>

### INTRODUCTION

Adenosine triphosphate (ATP)-binding cassette (ABC) transporters are highly expressed in tumor cells, as well as in organs involved in absorption and

secretion processes, mediating the ATP-dependent efflux of compounds, both endogenous substances and xenobiotics, including drugs. Their expression and activity levels are modulated by the presence of inhibitors, inducers and/or activators (1). The first known human ABC transporter was

P-gp, which confers multidrug resistance (MDR) to anticancer drugs (2). P-gp is an ATP-dependent efflux pump encoded by the MDR1 gene in humans, known to mediate multidrug resistance of neoplastic cells to cancer therapy (3). P-gp plays an important role in drug transport in many organs. In the gut, P-gp pumps drugs back into the lumen, leading to decrease their absorption whereas P-gp transports medications into the urine to be excreted from the body in kidneys (4).

Drug-drug interactions between substrates and P-gp inhibitors can modify the drug's pharmacokinetics by increasing bioavailability and organ uptake leading to more adverse drug reactions and toxicities. Possibly, coadministration of substrates for P-gp and P-gp-inducing agents may lead to a reduction in the levels of plasma drug and consequently reduce the effect of the treatment (5).

P-gp modulation -mediated transport has significant pharmacokinetic P-gp substrates implications. Changes in substrate pharmacokinetics may have the potential to alter the duration and magnitude of pharmacodynamics. It is important to understand P-gp modulation in order to predict the degree of which P-gp modulation may affect that substrate, minimize adverse effects or to get benefit from modulation of specific therapeutic advantage (6).

Captopril is an angiotensin-converting enzyme (ACE) inhibitor which was initially approved to treat high blood pressure and can be used alone or in combination with other antihypertensive drugs (7). The benefits of captopril in hypertension and heart failure result primarily from suppression of the renin-angiotensin-aldosterone system (RAAS) (8) and captopril causes many side effects including renal insufficiency, renal failure, nephrotic syndrome, polyuria, oliguria and urinary frequency as well as angina pectoris, myocardial infarction, Raynaud syndrome and congestive heart failure (9, 10).

Statins are a widely prescribed class of drugs that decrease cholesterol. Their mechanism of action is primarily via inhibition of HMG-CoA (hydroxymethylglutaryl-coenzyme A) reductase and the rate-limiting enzyme in the cholesterol biosynthesis pathway (11). Many side effects of statin drugs that can be more serious sometime including new-onset type 2 diabetes mellitus, hepatotoxicity, renal toxicity, and other conditions (12).

Spironolactone is an aldosterone antagonist, and a potassium-sparing diuretic are used for treatment of hyperaldosteronism and edematous states including congestive heart failure and liver cirrhosis (13). It causes common undesirable effects (>10%): CNS disturbances (drowsiness, lethargy, confusion, headache, fever, ataxia and/ or fatigue), GI disturbances including anorexia, dyspepsia, nausea, vomiting, peptic ulceration and/or colic (14).

The aim of this study was to investigate and compare the interaction between P-gp inducer spironolactone (SN) or

inhibitor captopril (CP) with its common substrate lovastatin (LV) after acute and chronic administration in rats and to determine the possibility of existence accumulation or not after chronic administration of three drugs.

## MATERIALS AND METHODS

### Animals and Conditions

A total of one hundred and thirty adult male albino rats were obtained from animal house of college of veterinary Medicine, University of Baghdad. They aged over 3 months and weighed 200-250 g. were used to perform different studies. They were fed standard pellet diet and drank tap water. The animals were left in special cages with good conditions in the animal house of College of veterinary medicine for two weeks for adaptation; maintained with standard condition at 10 / 14 h light-dark cycle, temperature at 20-25 °C in an air-conditioned room; and bed was mulch that changed twice weekly. Ethical approval was gotten from the care and use animal committee of the college of veterinary medicine/ university of Baghdad to start the work

The procedures used in this study were reviewed and approved by the scientific committee at the University of Baghdad's College of Veterinary Medicine in compliance with animal welfare ethical standards.

Forty mature, local breed rabbits, about 1.5-2 kg in weight of both sexes were used in this study, managed under the same conditions. Partial injury to semimembranosus muscle tendon was induced. Rabbits were divided into five equal groups; four of them (A, B, D, E) were irradiated with low-power laser at 5, 8, 15, 21 days postoperatively, whereas group (C) was left without irradiation and was considered as a control

### Assessment of Median Lethal Dose (LD<sub>50</sub>)

Forty rats were allocated into five groups according to the used treatment (captopril, spironolactone, lovastatin, captopril+lovastatin and spironolactone+lovastatin) using up and down method to determine their orally acute LD<sub>50</sub>. The drugs of this study were purchased from Y.S.P. Industries- Malaysia for lovastatin, Actavis-UK for spironolactone, and Medochemie-Cyprus for captopril.

Ranges of doses of LD<sub>50</sub> study were 3600-4400 mg/kg for captopril, 900-1100 mg/kg for spironolactone, and 4400-6000 mg/kg for lovastatin. The solution of the captopril dose was prepared by dissolving 1 tablet of captopril (50 mg) to 143 mL distill water to get concentration of (0.35 mg/mL) and to be given at dose volume 0.2 mL/100 g. of body weight of the animal. The dosing solution of spironolactone was also prepared by dissolving 1 tablet of spironolactone (100 mg) to 143 mL distill water to get concentration of (0.7 mg/mL) and was

given at dose volume 0.2 mL/100 g. of body weight of the animal. The dosing solution of lovastatin was prepared by dissolving 1 tablet of lovastatin (40 mg) to 138 mL distill water to prepare concentration of (0.29 mg/mL) and was given at dose volume 0.2 mL/100 g. of body weight of the animal.

Toxicity study was conducted according to the up and down method. This experiment was rendering for dosing of rats in singly of sequence at twenty four-hour intervals, together with dose of the initial set at "the toxicologist's best estimation of the LD<sub>50</sub>. Then the dose after each death was lowered; next each survival, the dose was raised, according to a prespecified progression factor of dose. If a death follows up an initial trend of raising doses of 10-20% or by constant factors a survival follows up an initial direction of lowering dose with an equivalent ratio, three additional animals were tested following an equivalent dose adjustment pattern then test was ended. The LD<sub>50</sub> were determined depending on Up and Down method and calculated by using the subsequent equation (15, 16):

$$LD_{50} = X_f + K_d$$

Where, X<sub>f</sub> = final dose administered, K=constant factor, and d= variation between levels of dose.

### Chronic Study

Ninety rats were used in the study of chronic administration, in which animals were divided equally into six groups according to oral daily doses regimen as following G1, control group, administered distilled water; G2, administered captopril at 0.7 mg/kg BW; G3, administered spironolactone at 1.4 mg/kg BW; G4, administered lovastatin at 0.57 mg/kg BW; G5, administered spironolactone at 1.4 mg/kg BW and lovastatin at 0.57 mg/kg BW; G6-administered captopril at 0.7 mg/kg BW and lovastatin at 0.57 mg/kg BW.

### Isobolographic Study

Isobolographic analysis and chronicity index ordinarily were used to determine the interaction sort of the three drugs, during which a line draw to affix the LD<sub>50</sub> of every 2 drugs studied in isobolograph and a point of intersection

determined by draw of lines vertically from the LD<sub>50</sub> values of everycombined drug.

The conclusion of interaction of drugs decided accordingly to the position of the spot of the two drugs joined LD<sub>50</sub> line. If the spot was besides right, it meant there was an antagonistic effect >1, besides left, meant potentiation or synergistic effect <1, but on the road=1, it meant there was an additive effect between the 2 drugs. The type of interaction estimated consistent with the subsequent equation (17):

$$\frac{a}{A} + \frac{b}{B} = 1$$

Where, a and b are chronic or acute (combined) LD<sub>50</sub> of drug 1 and 2, respectively; and A and B are chronic or acute (alone) LD<sub>50</sub> of drug 1 and 2, respectively.

### Chronicity Index

Chronicity index considered as the possibility measurement of accumulation of the drug after its chronic administration supporting comparison of the ratio of LD<sub>50</sub> values after acute and chronic administration to the drugs consistent with the equation:

$$\text{Chronicity index} = \frac{\text{LD}_{50} \text{ after acute dose}}{\text{LD}_{50} \text{ after 3 months administration of sublethal dose}}$$

If a value exceeded one, the accumulation possibility existed (18).

## RESULTS

### Acute Toxicity Study of P-gp Inhibitor and Substrate

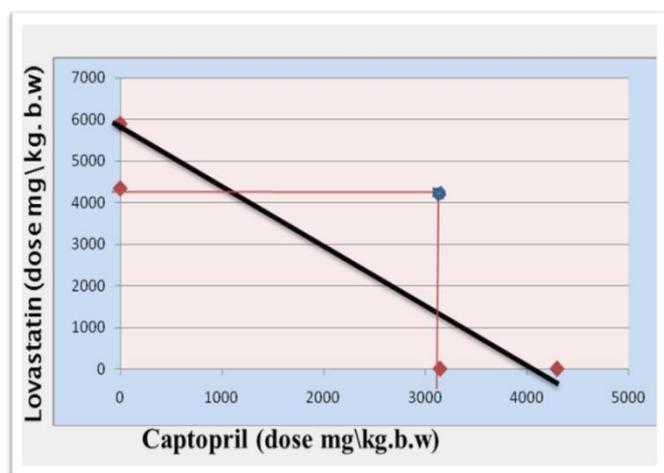
Results of acute toxicity found that LD<sub>50</sub> for captopril and lovastatin according to procedure of Dixon were 4294.8 and 5896.4 mg/kg BW respectively which reduced after their interaction to 3144.4+4344.4 mg/kg BW (Table 1).

Isobolographic analysis (Figure 1) revealed that LD<sub>50</sub> levels of captopril and lovastatin are intersected after the coadministration of both (to the right of the line that joined values of LD<sub>50</sub> of each of the above drugs solely

**Table 1.** LD<sub>50</sub> of captopril, lovastatin with their interaction of the acute toxicity study<sup>1</sup>

Groups	Initial dose	Last dose	Doses Difference	K value	Results after 24 h*	LD <sub>50</sub> **
captopril	3600	4000	400	0.737	00X0X0	4294.8
lovastatin	4400	5600	400	0.741	00000X0X0	5896.4
captopril+lovastatin	4000+5200	2800+4000	400+400	-0.861	XX0XX0	3144.4+4344.4

\*O=Survival animal, X=Dead animal. \*\*LD<sub>50</sub>= X<sub>f</sub>+K<sub>d</sub>, where: X<sub>f</sub>=final dose; K (constant) =0.860, d= differences between doses (Dixon, 1980). <sup>1</sup>All doses are in mg/kg BW



$$(a/A) + (b/B) \longrightarrow (3144.4/4294.8) + (4344.4/5896.4) = 1.4$$

This result indicated that there was an antagonistic effect of toxicity after the captopril and lovastatin combination of the acute administration.

**Acute toxicity study of P-gp Inducer and Substrate**

Acute toxicity showed that LD<sub>50</sub> for spironolactone and lovastatin according to Dixon procedure were 1174 and 5896.4 mg/ kg BW. respectively which were reduced after their interaction to 526 +3703.6 mg/kg BW (Table 2).

Isobolographic analysis: (Figure 2) showed that the intersected lines of LD<sub>50</sub> of spironolactone and lovastatin after combined administration was near the line of those joined values of LD<sub>50</sub> of only 2 drugs.

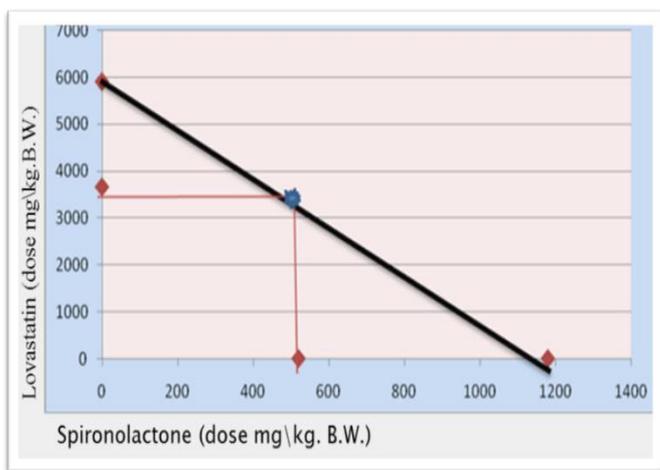
**Figure 1.** Isobolographic for interaction of acute toxicity between captopril and lovastatin

By applying Tallarida equation, the result was:

**Table 2.** LD<sub>50</sub> of spironolactone, lovastatin and their interaction of the acute toxicity study<sup>1</sup>

Groups	Initial dose	Last dose	Doses Difference	K value	Results after 24 h*	LD <sub>50</sub> **
Spironolactone	900	1100	100	0.741	OOXOXO	1174
Lovastatin	4400	5600	400	0.741	OOOXXOXO	5896.4
Spironolactone+Lovastatin	900+5200	600+4000	100+400	0.741	XXXXOXOX	526+3703.6

\*O=Survival animal, X=Dead animal. \*\*LD<sub>50</sub>= X<sub>f</sub>+K<sub>d</sub>, where: X<sub>f</sub>=final dose; K (constant) =0.860, d= differences between doses (Dixon, 1980). <sup>1</sup>All doses are in mg/kg BW



$$(a/A) + (b/B) \longrightarrow 1 = (3703.6/5896.4) + (526/1174)$$

The results explained that the acute toxic effect was as an additive after the spironolactone and lovastatin combination of acute administration

**Chronic Administration LD<sub>50</sub> of P-gp Inhibitor and Substrate**

Chronic toxicity studies explained that LD<sub>50</sub> for captopril and lovastatin after the trial end (90 days) according to method of Dixon were 2462.8 and 5200 mg/kg BW respectively that decreased after their combined administration to 861.6+ 2861.6 mg/kg BW (Table 3).

Isobolographic analysis (Figure 3) revealed that the lines of LD<sub>50</sub> levels of captopril and lovastatin intersected after their coadministration together was to the left of the line that joined values of LD<sub>50</sub> of each both drugs.

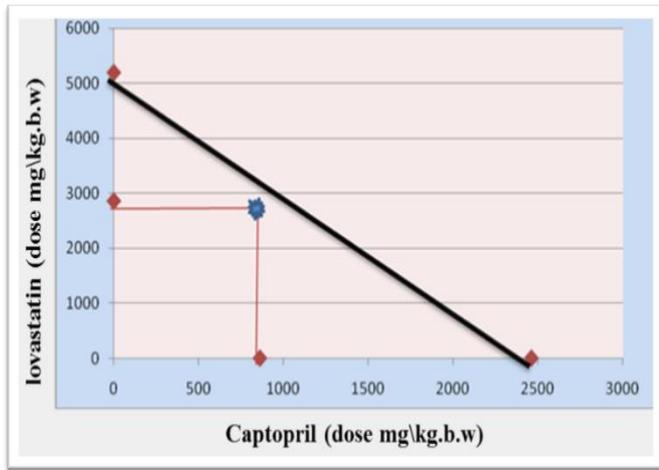
**Figure 2.** Isobolographic for interaction of acute toxicity between spironolactone and lovastatin

BY applying Tallarida equation, the result was:

**Table 3.** LD50 estimation for captopril, lovastatin and their interaction in study of chronic toxicity

Groups	Initial dose	Last dose	Doses Difference	K value	Results after 24 h*	LD <sub>50</sub> **
captopril	3200	2400	400	-0.157	XOXXX	2462.8
lovastatin	5000	4600	400	1.5	OOXXXO	5200
captopril+lovastatin	2000+4000	800+2800	400+400	-0.154	XXOXXX	861.6+2861.6

\*O=Survival animal, X=Dead animal. \*\*LD<sub>50</sub>= X<sub>f</sub>+K<sub>d</sub>, where: X<sub>f</sub>=final dose; K (constant) =0.860, d= differences between doses (Dixon, 1980). <sup>1</sup>All doses are in mg/kg BW



$$(a/A) + (b/B) \longrightarrow (2861.6/5200) + (861.6/2462.8) = 0.8$$

The result of chronic isobolographic interaction between the two drugs captopril and lovastatin had synergistic effect.

**Chronic Administration LD<sub>50</sub> of P-gp Inducer and Substrate**

Chronic toxicity studies exhibited that LD<sub>50</sub> for spironolactone and lovastatin after the end of study (90 days) according to Dixon method were 850 and 5200 mg/kg BW, respectively, that decreased after their coadministration to 762.8+3851 mg/kg BW (Table 4).

Isobolographic analysis (Figure 4) exhibited the lines of LD<sub>50</sub> of spironolactone and lovastatin intersected after their coadministration together was to the right of the line that joined values of LD<sub>50</sub> of each two drugs.

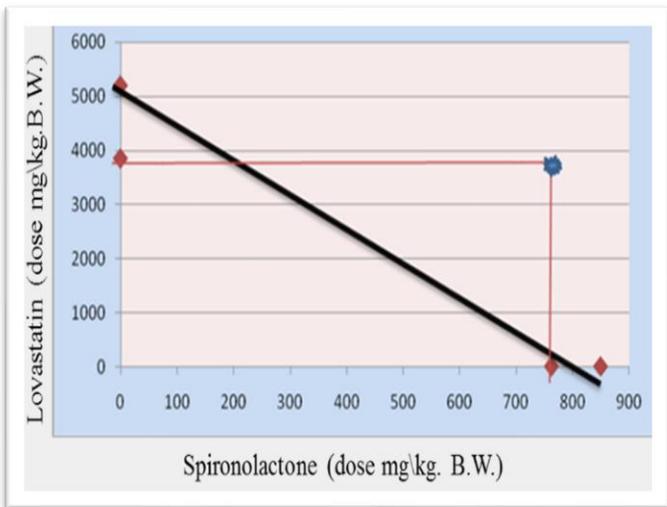
**Figure 3.** Isobolographic for chronic toxicity interaction between captopril and lovastatin

By applying Tallarida equation, the result was:

**Table 4.** Determination of LD<sub>50</sub> for spironolactone, lovastatin and their interaction in study

Groups	Initial dose	Last dose	Doses Difference	K value	Results after 24 h*	LD <sub>50</sub> **
spironolactone	800	700	100	1.5	00XXXO	850
lovastatin	5000	4600	400	1.5	00XXXO	5200
spironolactone +lovastatin	900+4400	800+4000	100+400	0.372	XXOXX	762.8+3851

\*O=Survival animal, X=Dead animal. \*\*LD<sub>50</sub>= X<sub>f</sub>+K<sub>d</sub>, where: X<sub>f</sub>=final dose; K (constant) =0.860, d= differences between doses (Dixon, 1980). <sup>1</sup>All doses are in mg/kg BW



**Figure 4.** Isobolographic for chronic Toxicity interaction between spironolactone and lovastatin

By applying Tallarida equation, the result was

$$(a/A) + (b/B) \longrightarrow (762.8/850) + (3851/5200) = 1.6$$

The result of chronic isobolographic interaction between the two drugs spironolactone and lovastatin had antagonistic effect

**Chronicity index (CI)**

Results of chronicity index are presented in Table 5. Index of chronicity was measured consistently with LD<sub>50</sub> after chronic and acute administration of different treatments by employment the following equation to determine the possibility of accumulation after chronic administration.

**Table 5.** Chronicity index of P-gp inhibitor and inducer

P-gp inhibitor and substrate	Administered	CI
captopril	alone	1.70
lovastatin	alone	1.13
captopril	combined	3.60
lovastatin	combined	1.50
P-gp inducer and substrate		
spironolactone	alone	1.50
lovastatin	alone	1.13
spironolactone	combined	0.70

**DISCUSSION**

Interaction of such used drugs in the study were possible since both captopril and spironolactone used in the therapy of high blood pressure while lovastatin usually used to overcome high lipid and cholesterol that is caused by the high blood pressure. Study of acute toxicity is

important to compare between the drugs for understanding types of interaction according to isobolographic study and then chronicity index that possibly explain the accumulation or decreasing of drugs in the body tissues. Chronic study was used to know the effects of these drugs during long periods of treatment.

The present study was designed and performed for the first time in Iraq to study the interaction between p-glycoprotein inhibitor (captopril), P-glycoprotein inducer (spironolactone) and its substrate (lovastatin) and to investigate its toxicological effect consequence of using therapeutic doses for all drugs by performing acute and chronic studies with isobolographic interaction studies and chronicity index. P-gp influences the pharmacokinetics of its substrate drugs due to its poly specific binding nature and its expression in many physical barriers and pharmacokinetics related organs (i.e., the gastro-intestinal (GI) tract, blood-brain-barrier (BBB), kidney, liver, endothelium and placenta) that function to limit the cellular uptake, distribution, excretion and toxicity of many substances and xenobiotics (19).

The results of isobolographic analysis showed that the sort of interaction between P-gp inhibitor (captopril) and lovastatin in groups of alone and combined administration were antagonistic after acute administration while it was synergistic after chronic administration. For P-gp inducer spironolactone and lovastatin, it showed additive after acute administration and antagonistic after chronic administration. Chronicity index results showed that both captopril and lovastatin were accumulated after giving alone and were more after their combined administration while the chronicity index for P-gp inducer (spironolactone) and lovastatin showed less total concentration in the body burden after their combined administration than giving alone.

These results explained the sort of interaction between P-gp inhibitor and inducer with their common substrate lovastatin (20). Lin, 2003 showed that P-gp could be viewed as a unique defensive barrier network against the entry of xenobiotics into the body. This efflux carrier decreased the bioavailability of administered drugs by preventing their sufficient accumulation intracellularly, so the efficacy of drugs had to be lowered. It also altered the pharmacokinetics and pharmacodynamics of its substrates.

So it played an important role in first-pass elimination of orally administered drugs to limit their bioavailability by effluxing drugs from the lumen-facing epithelia of the small intestine and colon, and from the bile-facing canaliculi of the liver. It eliminated substrates from the systemic circulation at the urine-facing side of the brush border membrane of proximal tubules in the kidney, and again through biliary excretion. It restricted the permeability of drugs into 'sanctuary' organs from the apical or serosal side of BBB (e.g., blood-brain, blood-cerebral spinal fluid, blood-placenta, blood-testis barriers) (21). These results

agreed with (22) who explained the drug-drug interaction between inhibitors of P-glycoprotein and its substrates leading to modification in pharmacokinetics and thus increased in bioavailability and organ uptake leading to more adverse drug reactions and toxicities. While interaction between P-gp inducer and its substrate led to a reduction in plasma drug levels and consequently reduction in efficacy of drug. Our results were in agreement with (23) Glaeser, 2011 who pointed the induction or inhibition of P-glycoprotein might cause drug-drug interactions. Results of coadministration of P-gp inhibitor or inducer with their common substrate were corresponding with (24) Lund et al., 2017 who explained the administration of combined drugs that inhibited or induced P-gp might increase or decrease body substrate concentration, respectively, the systemic exposure of P-gp substrates. As mentioned by Zhou, 2008(25) altered P-gp activity due to induction and/or inhibition can cause drug-drug interactions with modification drug pharmacokinetics and response.

It seems from the result of chronicity index of both giving alone and combined administration of P-gp inhibitor and substrate that captopril possibly acted as both inhibitor and substrate since it showed more accumulation after chronic administration (3.6) for captopril but (1.5) for lovastatin. This explained by the increase in intestinal absorption and decrease in biliary and renal excretion due to the inhibition of P-gp transmembrane function by captopril in contrast P-gp inducer (spironolactone) caused reduction in body burden concentration similar to that of its substrate (lovastatin) after their combined administration to 0.7 and 0.9 times due to the increase in P-gp kinetic effects.

It can be concluded that P-gp inhibitor (captopril) may cause accumulation of itself and substrate (lovastatin), while P-gp inducer (spironolactone) possibly cause reduction in the body burden of itself as well as lovastatin due to their effects on the kinetics of the body and this may affect on efficacy and safety of drugs.

So care must be taken to the therapeutic dose of substrate, where it must be decreased or increased after its chronic coadministration with P-gp inhibitor or inducer.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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## دراسة التداخل السمي بين مثبط البروتين السكري-بي (كابوتوبريل) ومحفزه (سبيرونولاكتون) مع الركييزة (لوفاستاتين) في ذكور الجرذان

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### الخلاصة

تم دراسة التداخل السمي لتقييم ومقارنة تأثير مثبط البروتين السكري-بي (كابوتوبريل) والمحفزه (سبيرونولاكتون) مع الركييزة المشتركة (لوفاستاتين) التي تمت من خلال مقارنة الجرعة القاتلة النصفية من الدراسة الحادة مع تلك التي تم الحصول عليها بعد اعطاء الجرعات العلاجية المزمنة للأدوية المستخدمة (منفردة و مشتركة) لمدة 90 يوماً. لذلك، تم استخدام التحليل الأيزوبولوجرافيا ومعامل الأمان كمؤشر لهذه الدراسة. تم تقسيم 40 من الجرذان إلى خمس مجاميع تبعاً للعلاجات المستخدمة (كابوتوبريل، سبيرونولاكتون، لوفاستاتين، كابوتوبريل + لوفاستاتين، سبيرونولاكتون + لوفاستاتين) وباستخدام طريقة الصعود والنزول لتحديد الجرعة النصفية المميتة لتلك الأدوية. في حين تم استخدام 90 من الجرذان للدراسة المزمنة قسمت إلى ست مجاميع و جرعت يوماً على طريق الفم كالاتي: المجموعة الأولى: مجموعة السيطرة تم اعطائها الماء المقطر، المجموعة الثانية: أعطيت الكابوتوبريل بجرعة 0,7 ملغم/كغم من وزن الجسم، المجموعة الثالثة: أعطيت السبيرونولاكتون بجرعة 1,4 ملغم/كغم من وزن الجسم، المجموعة الرابعة: أعطيت اللوفاستاتين بجرعة 0,57 ملغم/كغم من وزن الجسم، المجموعة الخامسة: أعطيت السبيرونولاكتون بجرعة 1,4 ملغم/كغم من وزن الجسم و اللوفاستاتين بجرعة 0,57 ملغم/كغم من وزن الجسم، المجموعة السادسة: أعطيت الكابوتوبريل بجرعة 0,7 ملغم/كغم من وزن الجسم و اللوفاستاتين بجرعة 0,57 ملغم/كغم من وزن الجسم. بينت نتائج تحليل الأيزوبولوجرافيا نوع التداخل بين مثبط البروتين السكري-بي الكابوتوبريل و اللوفاستاتين بإعطائهما منفرداً و معاً حيث كان التأثير مضاداً بعد التعرض الحاد بينما كان تازرياً بعد التعرض المزمن لمدة 90 يوم. بينما كان تأثير محفز البروتين السكري-بي السبيرونولاكتون و اللوفاستاتين تأثيراً مضاداً بعد التعرض الحاد و مضاداً بعد التعرض المزمن لمدة 90 يوم. حيث بينت نتائج مؤشر الأمان ان هناك تراكم للمثبط كابوتوبريل و اللوفاستاتين بعد اعطائهما منفردات و أكثر تراكماً عند اعطائهما سوياً. بينما أوضحت نتائج مؤشر الأمان للمحفز السبيرونولاكتون و اللوفاستاتين قلة في التركيز الكلي في عيب الجسم بعد الاعطاء المشترك أكثر من الإعطاء المنفرد. في الاستنتاج يبدو ان مثبط البروتين السكري-بي الكابوتوبريل يسبب تراكم لنفسه و للركييزة (لوفاستاتين) في الجسم. في حين ان المحفز السبيرونولاكتون نفسه يسبب تخفيض في عيب الجسم بالإضافة إلى اللوفاستاتين و الذي من المحتمل ان يكون نتيجة تأثيرهما على الحركة الدوائية داخل الجسم والتي ستؤثر على فعالية و سلامة الأدوية.

الكلمات المفتاحية: البروتين السكري-بي، المحفز، المثبط، الركييزة، الجرعة القاتلة النصفية