ISSN 2664-4142 (Print) & ISSN 2664-6749 (Online)
South Asian Research Journal of Pharmaceutical Sciences
Abbreviated Key Title: South Asian Res J Pharm Sci

| Volume-6 | Issue-4 | Jul-Aug 2024 | **DOI: https://doi.org/10.36346/sarjps.2024.v06i04.005**

Original Research Article

Single and Combinations of Rosuvastatin, Celecoxib, and Colchicine Effects on Biochemical and CBC Parameters of Wistar Albino Rats

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Article History
Received: 30.06.2024
Accepted: 06.08.2024
Published: 12.08.2024

Abstract: Drug resistance became a well-known problem in different areas of pharmacology, including anti-cancer therapy and antibiotics. The overcoming of drug resistance either by different drugs or doses, increases the risk of tissue toxicity. The combination of single FDA-approved drugs became one of the solutions shorting the time for new drug approval, and lowering the cost of manufacturing and transporting of drug to pharmacy shelves. Every day a new combination is investigated to narrow the gap in different pharmacological requirements. Lipid-lowering and anti-inflammatory drugs are widely used and are widely available globally. The study aimed to investigate four probabilities of combinations of three single drugs Rosuvastatine (Ro), Celecoxib (Ce), and Colchicine (Co) on biochemical and Complete Blood Count parameters (CBC) to evaluate the reliability and probable effects of these drugs on normal body function. Nine groups (n=6) of Wistar Albino Rats were inoculated with single and combinations of drugs for eight days using the maximum normal human doses of each drug, blood samples were collected in the middle, and at the end of the experiment. Results showed that combinations induced abnormal biochemical, and CBC parameters in ALT, AST, Creatinine, and RBC parameters in all but one (Rosuvastatine-Celecoxibe-Colchicine) of the combination. The study concluded that the combination could be used except that showed a higher level of abnormal physiological parameters, and percussions should taken by more pharmacological and physiological investigation in a bigger scale of studies including longer durations and different animal models before the combinations utilized by human.

Keywords: Drug, pharmacology, Manufacturing, RBC.

INTRODUCTION

Drug combination is an important strategy in pharmacology to reduce the drug resistance phenomena and reduce the toxic effect and cost of treatment by lowering the therapeutic doses, and combining drugs for specific uses it is important to evaluate the probable effects and consequences of this combination to use the combination accordingly (Plana, Palmer and Sorger, 2022). Efforts were made to predict the effect and relation of drugs when combined. Although good data were collected the field of combination is still undiscovered due to the huge number of chemical compounds and individual variations (Menden *et al.*, 2019). Rosuvastatin a drug of a group known as statin prescribed for lipid lowering in hyperlipidemia patients acts by inhibiting the hydroxy methylglutaryl coenzyme A (HMG-CoA) reductase (Fan *et al.*, 2020; Schumacher and Debose-boyd, 2021). Celecoxib is an anti-inflammatory drug classified as a COX-2 inhibitor that reduces inflammation by inhibiting of cyclooxygenase 2 enzyme (Cruz *et al.*, 2022). Colchicine is an alkaloid Food and Drug Administration (FDA) approved compound used for the treatment of gout and inflammations (Deftereos *et al.*, 2022). Oxidation and cytotoxicity induced by drugs and any compound that leads to hepatic and renal malfunctions could be evaluated by several means including the lipid profile and liver enzymes (Awad and Kamel, 2010; Preusch *et al.*, 2010; Ansari *et al.*, 2012; Dodiya *et al.*, 2013; Xilifu *et al.*, 2014). Human and animal normal and pathological levels of CBC and biochemical parameters are well known and any changes could be monitored and easily diagnosed using different methods (Pozdnyakova *et al.*, 2021; Vigneshwar *et al.*, 2021). Although researchers made appreciated efforts in monitoring the probable effects of every single FDA-approved drug used in the current study, the combinations could induce new parameters changes as a result of complex unpredictable actions and interaction of new combinations (Awad and Kamel,

2010; Koçkaya *et al.*, 2010; Ansari *et al.*, 2012; Dodiya *et al.*, 2013; Kale, Oyesola and Raji, 2018; Sulimani, Yousef and Mohamed, 2021). This is the first study in a unique design that uses these three important drugs and it's all probable (four) combinations at the max normal therapeutic doses with positive (DMSO) and negative control to evaluate the biochemical and cellular effects on Wistar Albino Rats.

MATERIALS AND METHODS

Nine groups of Wistar Albino Rats were housed in the animal breeding house of the College of Veterinary Medicine at Tikrit University. Each group had six animals each animal weight about 200g. The groups were named G1, G2, G3, G4, G5, G6, G7, G8, C treated with Rosuvastatine, Celecoxib, Colchicin, Rosuvastatine-Celecoxib, Rosuvastatine-Colchicin, Celecoxib-Colchicin, Rosuvastatine-Celecoxib-Colchicin, DMSO as control positive, and Normal saline as control negative the animals were housed for eight days at the age of four months old. At the time of experiment the which extended for eight days blood was collected from the orbital plexuses of the eye on day four and from the heart after anesthesia using chloroform on day nine. All the animals were fed on normal pellets and the water was withdrawn only six hours before the treatments were induced. Each animal received the maximum human doses of each drug Rosuvaststine 40mg, Celevocibe 400mg, and Colchicine 1.2mg (Jones *et al.*, 2003; Adams, Sekhon and Wright, 2014; Kale, Oyesola and Raji, 2018; Liu *et al.*, 2024; Sadiq, Robinson and Terrell, 2024). The doses convert to Rats using a 6.17 conversion rate and suggest a median human weight of 60kg. The daily doses were divided into two shots dissolved in DMSO and administrated orally using disposable 0.5ml isoline syringes(Cavas, Beltrán and Navarro, 2005; Galvao *et al.*, 2014; Ahmed *et al.*, 2022; Fang, Zheng and He, 2023). At the middle end of the experiment, blood was collected from the eye using a gel tube, and the serum was collected by centrifugation at 3500 rpm for 5min before being stored at -20C^{o}, at the end of the experiment blood was collected from the heat using gel tube for serum and tubes with EDTA for whole blood. The blood was sent directly for CBC analysis where the serum was kept at -20C^{o} for biochemical test analysis. The CBC was made using an Auto Hemato analyzer, while the biochemical test was performed by using a Spectrophotometer and colorimetric kits (Shakeri, Soukhtanloo and Boskabady, 2017). Results were analyzed and graphs were made by using GraphPad Prism software and a one-way ANOVA test.

RESULTS

The results of the eight biochemical parameters table (1-1) showed non-significant changes for Triglycerides, Cholesterol, HDL, Albumin, and Urea in all groups in both four and eight days of treatment groups. The Creatinin, AST, and ALT showed a significant increase in the level at both four and eight days of experiment for single and combination groups of treatment. The Creatinen results were non-significant at G2 and G3 single drug treatment at day four and G1, G2, and G3 of day eight treatment, while all the combinations had significant increases in Creatinen levels at both four and eight days of the experiment. The AST had non-significant effects only in G1 and G3 on day four of treatment, while G3 was the only group of treatments that showed non-significant effects on day eight of the experiment. The ALT showed non-significant results only at G1 during day four, and G7 showed non-significant results at both four and eight days of treatment. The G8 of DMSO treatment was non-significant in all parameters. All the CBC parameters were non-significant except in RBC, HCT, and HGB of G5 and HCT and HGB of G2.

Table 1-1: Treatment effect on biochemical parameters. (A)= day 4, (B) = day 8, (*)= P<0.05, (**)= P<0.01, (***)= P<0.001, (****)= P<0.0001

No	Parameter	G1	G2	G3	G4	G5	G6	G7	G8	C
1	Albumin (A)	1.99	1.82	1.75	1.85	2.01	1.94	1.81	1.98	1.87
2	Albumin (B)	1.89	2.06	1.86	1.92	1.79	1.88n	1.80	1.95	1.88
3	Creatinine (A)	0.68*	0.50	0.32	0.67*	0.68*	0.74**	0.67*	0.49	0.44
4	Creatinine (B)	0.36	0.27	0.31	0.75*	0.74*	0.81**	0.77*	0.55	0.45
5	Urea (A)	27.20	26.47	22.04	22.00	23.61	26.24	25.59	26.62	28.21
6	Urea (B)	27.20	26.02	22.37	26.85	25.35	25.08	26.09	24.14	28.72
7	AST (A)	14.54	25.59****	19.19	47.11****	61.07****	46.00****	35.7****	11.02	14.03
8	AST (B)	29.37****	24.13****	21.49	51.47****	74.16****	121.56****	100.04****	14.83	17.03
9	ALT (A)	11.92	15.41**	20.06****	22.10****	13.96	27.33****	13.79	12.50	10.25
10	ALT (B)	20.10*	21.52**	27.04****	35.19****	25.59****	28.21****	16.57	19.48	15.72
11	Triglyceride (A)	90.56	71.21	86.93	72.44	112.77	102.38	78.36	101.14	77.21
12	Triglyceride (B)	82.45	97.33	94.18	84.17	106.29	94.28	86.65	101.52	78.02
13	Cholesterol (A)	91.01	66.81	64.51	76.99	74.26	73.16	69.66	73.60	68.24
14	Cholesterol (B)	80.17	72.39	57.83	76.01	69.98	68.34	59.80	83.13	68.31
15	HDL (A)	56.49	55.44	55.31	55.51	56.16	55.18	55.44	55.44	56.36
16	HDL (B)	56.36	56.42	57.46	56.81	55.96	55.64	55.47	56.09	57.01

Table 1-2: Treatment effect on CBC parameters. (A)= day 4, (B)= day 8, (*) = P<0.05, (**) = P<0.01, (***) = P<0.001, (****) = P<0.0001

No	Parameter	G1	G2	G3	G4	G5	G6	G7	G8	C
1	RBC	4.98	4.79	4.80	4.84	4.23**	5.07	4.90	4.68	5.93
2	HCT	33.5	31.05*	32.55	32.85	28.53**	33.65	33.68	31.96	38.50
3	HGB	11.08	10.15*	10.78	10.63	9.41***	10.98	10.95	10.60	12.70
4	MCV	67.76	65.05	68.5	68.23	67.51	66.46	69.25	68.65	64.95
5	MCH	21.2	20.3	21.6	21.6	22.6	20.1	23.6	22.4	21.6
6	MCHC	33	32.83	32.83	32.33	33.16	32.5	32.5	33	33
7	WBC	19.97	16.14	18.29	20.15	20.19	18.06	18.52	20.14	21.69
8	PLT	665.33	622.16	558.16	632.5	539.33	711.83	668	667.83	498
9	Lymphocyte	64.46	58.63	70.34	68.54	63.15	63.71	69.55	64	61.69
10	Monocyte	11.24	14.16	12.75	13.28	14.76	15.03	14.18	11.51	10.47
11	Neutrophil	19.26	24.32	13.77	15.13	19.81	18.88	14.07	21.92	23.94
12	Basophil	0.24	0.16	0.16	0.22	0.12	0.21	0.14	0.16	0.13
13	Eosinophil	3.70	2.71	2.91	2.82	2.14	2.14	2.04	2.23	3.76

DISCUSSION

The results of the current study showed the effect of four combinations of three drugs compared to control and single drugs. The results of Rosuvastatin used in the current study agree with other researchers at different doses and duration of experiments. Three levels of doses including very low at human doses of 10 mg/kg/day, low at 20 mg/kg/day, and high at 40 mg/kg/day at durations of 7, 14, 21, and 28 days of the experiment, all of these results showed the same results about Rosuvastatin. Rosuvastatin showed no effect on lipid profile and a marginal effect on liver function and oxidative stress parameters including AST and ALT (Awad and Kamel, 2010; Preusch *et al.*, 2010; Ansari *et al.*, 2012; Dodiya *et al.*, 2013; Xilifu *et al.*, 2014). The results of Celecoxib also agree with other researchers' results who showed that the cytotoxic effect of Celecoxibe appeared after 28 to 30 days at the dose of 50 mg/kg/day as an increase in liver oxidative enzymes and no effect was shown at lipid profile and all the biochemical test will show a normal level at the day 7 of administration (Koçkaya *et al.*, 2010; Kale, Oyesola and Raji, 2018; Sulimani, Yousef and Mohamed, 2021). The eight days experiment designed for clinical uses of Celecoxib and it is known that Celecoxib's effective point of treatment was between 5-7 days and the experiments designed for more than 7 days investigated other preposes than for clinical use of the drug (Xu *et al.*, 2021). At the same time, the Colchicine beneficial effect could reached by using the 1.2 mg\day for eight days (Chappey and Scherrmannl, 1995; Liu *et al.*, 2024; Sadiq, Robinson and Terrell, 2024). The therapeutic effect of a single drug of colchicine in the current study agrees with other studies that have shown non-significant changes in lipid profile with changes in ALT level (Huang *et al.*, 2014; Emara *et al.*, 2021; Mahmood, Obaid and Abass, 2022). The DrugData bank shows that the combination of Celecoxib-Colchicine should be avoided due to interactions between the drugs that induce a toxic compound in body tissue *(Bonate et al., 1998; Kim & Moon, 2012; Otani et al., 2020;Wang et al.*, 2024; Yin & Wang, 2016). These notes agree with the current study where this group of combinations shed a highly significant increase in toxicity parameters of ALT, AST, and Creatinin. The Rosuvastatine-Celecoxibe combination not only increases the level of AST and ALT but the results of CBC also showed a significant decrease in RBC and as a consequence the HCT and HGB this decrement in the group of Rosuvastatine-Celecoxib which is explained as a result of the effect of both drugs on hematopoietic dynamic and movement arrest to the cells from bone marrow with calcium deficiency that is essential in contraction, both drugs also had a direct effect on mitotic division through cytoskeleton and centrosome deactivation (Deng *et al.*, 2022a; Houde *et al.*, 2017; Mahardhika *et al.*, 2022; Mengual *et al.*, 2022; Ohya & Ogura, 1993; Zhang *et al.*, 2019; Zhou *et al.*, 2023). The lowest combination showed the effect was the combination of G7 where it had a non-significant effect on ALT although it had a higher level of AST value. The elevation of ALT in G2, G3, G4, and G6 shows that these groups induced hepatotoxicity more than other groups were associated with other types of tissues (Smith *et al.*, 2020). The elevation of AST is also associated with liver damage in its acute stage but it is more related to muscular and renal tissue damage especially if the AST is associated with increased Creatinine levels G4, G5, G6, and G7 (Ndrepepa, 2021).

CONCLUSION

The combination of group 7 was the best formulation of combination, while the group 6 combination had the most significant negative effects on the physiological profile, especially the liver AST and ALT. The other groups of the combination were in between these combinations.

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