Rafidain Journal of Science
https://rsci.uomosul.edu.iq

Vol. 34, No. 2, pp. 52-61, 2025 (June)

Metformin and Amoxicillin/Clavulanate as Co-Administration for the Treatment of Hyperglycemia in Female Rats Caused by Alloxan

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p-ISSN: 1608-9391
e -ISSN: 2664-2786

Article information

Received: 16/2/2025
Revised: 27/4/2025
Accepted: 7/5/2025

DOI: 10.33899/rjs.2025.187744

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ABSTRACT

Diabetes mellitus (DM) or hyperglycemia is spreading quickly worldwide. When infections coexist, the oral hypoglycemic medication metformin is co-administered with an antimicrobial agent. The current study examined the effects of co-administering Amoxicillin/Clavulanate (AMC) and metformin in female rats with alloxan-induced diabetes. AMC is an antibiotic used to treat inflammation. Rats used in the study were separated into five groups of five albino rats each. Tap water and the same meal were given to group I negative control without any treatment. Group II positive control administrations of alloxan monohydrate 200 mg/kg body weight allowance, recipients in group three receiving 625 mg of AMC over the course of two weeks, and recipients in groups four receiving metformin form in 500 mg/kg with alloxan A last group V recipient will take AMC, metformin, and alloxan for two weeks. On days 0, 7, and 14, measurements of serum glucose, total cholesterol, triglycerides, and electrolytes (Cl-, Na+, and K+) were made. Samples of blood were collected weekly and parameters were measured. Results revealed no discernible change in total cholesterol, triglycerides, or electrolytes chloride and potassium. When compared to rats treated with metformin and alloxan, animals treated with AMC. These results indicate that the glucose-depletion impact of metformin could be accelerated by co-administration with the AMC. Low levels of sugar and sodium have been observed of animals caused by diabetes with alloxan.

Keywords: Diabetes mellitus, hyperglycemic, amoxicillin/clavulanate, metformin, alloxan.

INTRODUCTION

Pyrazoles are important heterocyclic compounds due to their wide and intensive use in various fields, especially in medicinal and pharmaceutical chemistry (Kotnala *et al*., 2024). Also, pyrazole derivatives have different biological activity (Gwady *et al*., 2010) such as anticancer (Wang *et al*., 2020) antimicrobial (Desai *et al*., 2020) antiviral (Yang *et al*., 2021) antagonist (Harcken *et al*., 2019) analgesic (Aggarwal *et al*., 2020) anti-inflammatory (Nayak *et al*., 2020) antioxidant (Vagish *et al*., 2021) anthelmintic (Bhavsar *et al*., 2020) herbicidal (Shawkat and Omar, 2012) (Fu *et al*., 2020) and antimitotic activities (Zhang *et al*., 2020), Pyrazole was first prepared by the scientist Ludwig Knorr 1883 (Alam *et al*., 2015), Then many methods were developed to prepare pyrazole, one of these methods is the reaction of α,β-unsaturated carbonyl compounds with hydrazine hydrate. The thioester compound containing the active methylene group was relied upon to prepare α, β-unsaturated carbonyl compounds by reacting with aldehyde substituents (Al-Saheb *et al*., 2020). A lot of people have androgenic alopecia (AGA), which is a kind of male pattern baldness. (Koch *et al*., 2020). The factors that lead to AGA include an imbalance in androgen hormones, stress, genetic illnesses, starvation, an overactive 5α-reductase type II (5αR2), malfunction in the thyroid gland, addiction to drugs, and aging (Richards *et al*., 2008). Most androgens, including testosterone, are primarily produced by the testicles and converted to dihydrotestosterone (DHT) via 5αR2, pharmacological treatments using synthetic medications like finasteride or minoxidil, and hair follicle regeneration utilizing altered stem cells (Gupta *et al*., 2017). Androgenetic alopecia is treated by finasteride, which is an oral selective 5-alpha-reductase inhibitor (Mysore and Shashikumar, 2016). Severe dermatological adverse effects, such as decreased libido, irritation, itching, erythema, and depression, have been recorded with these medications (Yim *et al*., 2014). Therefore, it is critical to find a new pharmacological drug that promotes hair growth without causing any side effects. One possible method for developing future pharmaceutical treatments to treat a variety of diseases is computer-aided drug design (CADD), which has just come into its own (Llorach-Pares *et al*., 2022). In this case, we want to use a computational technique to discover new chemical compounds that might be used as 5αR2 inhibitors cure AGA.

MATERIALS AND METHODS

Compounds that were used in this study: All compounds were obtained from Aldrich, BDH, and Fluka companies. The melting point apparatus was recorded by Stuart (SPM30). Compounds determined and characterized by spectroscopy methods ^{1}H-NMR was recorded by DMSO-d6 at 400 MHz with TMS as the internal standards and Infrared (FT-IR) spectra were recorded using ATR-FTIR Spectrophotometer. The thin-layer chromatography (TLC) was carried out on an Eastman chromatogram sheet (20x20) cm, 13181 silica gel with the fluorescent indicator (No. 6060) with solvent system benzene: Methanol with a ratio of (8:2).

EXPERIMENTAL

Synthesis of (1,3-benzothiazol-2-yl) cyanoethanethioate (1)

Equal quantities (0.0239 mol) of 2-mercapto-benzothiazole were mixed with K_2CO_3 in dry acetone in a (250 ml) conical flask equipped with a magnetic stirrer for 30 min at laboratory temperature, followed by the gradually addition of (3.5 ml) of ethyl cyanoacetate. After the completion of the addition, the mixture was refluxed for (5 hours) and the reaction was monitored by TLC. After the reaction was completed, the mixture was cooled and filtered to get rid of the reaction residues. Then, the filtrate was placed under vacuum to get rid of the solvent and obtain the product, and it was recrystallized using ethanol absolute. ATR-FTIR:C≡N(2184); C=O(1660); C=N(1596); C-S(749) cm^{-1}.1H-NMR (400 MHz, DMSO) (ppm) 7.39 (d, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 7.9 Hz, 1H), 7.07 (s, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 3.97 (s,2H).

Synthesis of α, β-unsaturated carbonyl (2a-h) (Abu-Hashem and Gouda, 2017)

purchased from the animal house of the Iraqi center cancer and medical genetics, Baghdad, Iraq. Before commencing the experiment, the rats were acclimatized for seven (7) days under standard environmental conditions (temperature 25±2; relative humidity (RH) 50±5%; 12 hrs light/dark cycle). The animals were provided with food and water during the experimental period except that of the induction of diabetes where animals were fasted for 24 hours prior to the administration of alloxan (Ibegbulem and Chikezie, 2013).

Induction of experimental diabetes

One intraperitoneal injection of alloxan monohydrate, 200 mg/kg body weight, diluted in a 0.9% solution of sodium chloride, was given to induce type 1 diabetes (Shajeela *et al*., 2013). To avoid hypoglycemia after alloxan administration, rats were maintained on 6% glucose solution through drinker for 24 hours. Alloxan is capable of causing ultimate hypoglycemia as a result of enormous pancreatic release (Hamadi, 2012). The animals were applauded for blood glucose level 48 hours after alloxan injection, and blood sugar level above 300 mg/dl was used for the experiment.

Experimental design

A total of 25 rats were divided into five groups, each consisting of five rats. The following treatments were administered to the animals in each group:

Group I: Negative group, without therapy, they were given tap water and the same meal until the end of the study.

Group II: Positive group, IP injection of alloxan 200 mg/kg body weight.

Group III: Treated with AMC antibiotic 625 mg/kg body weight.

Group IV: IP injection of alloxan 200 mg/kg body weight+treated with metformin 500 mg/kg body weight.

Group V**:** IP injection of alloxan 200 mg/kg body weight+treated with metformin 500+AMC 625 mg/kg body weight.

Blood collection

At the end of the experiment, anesthetize the animals for a few seconds and then draw the blood from all groups weekly from a rat's eye orbital at 0, 7, and 14 days using a capillary glass tube and centrifuged at 2688 g for 5 minutes. The clear, non-haemolysed sera was separated and stored at (-20 C) for measurements of biochemical analyses (AL-Abachi and Al-Gorany, 2019).

Estimation of serum biochemical parameters

Glucose (Cat. No. 10121, 10260), total cholesterol (Cat. No.10017, 10018, 10028), triglycerides (Cat. No.10720p, 10724, 10725) were measured spectrophotometrically using ready kit (Human *Co.*) and several electrolytes, sodium (Na^+) (Cat. No. 1001387), potassium (K^+) (Cat. No. 1001390), and chloride (Cl^-) (Cat. No. 1001360), were among the serum biochemical markers examined by using ready kit (spinreact *Co*.).

Data analysis

The results of this study were expressed as mean± SD. IBM SPSS version 21.0 was used to perform the data analysis, statistical studies were carried out using the regression and ANOVA procedures, as well as the Tukey numerous pairwise comparison tests, with a probability threshold of $P \leq 0.05$ deemed significant. the use and interpretations of data was carried out in accordance to (Morgan *et al*., 2020).

RESULTS

(Table 1) and Fig. (1) shows the effects of CO-administration of AMC antibiotic with metformin on glucose, triglyceride (TG), and total cholesterol (TC) in rats with diabetes mellitus throughout a 14-days treatment period. The results appearance that glucose in the III, IV, V and I groups decreased significantly (131.90±5.81, 188.74±16.85, 207.21±22.93, 130.65±12.23

(P≤0.05)) respectively compared with that of diabetic control II group. The triglyceride (TG) is not significant that of diabetic control II group. Total cholesterol (TC) is not significant in all groups except the III group; it's decreased significantly about remainder groups.

Table 1: Serum glucose, triglyceride (TG) and total cholesterol (TC) in negative and positive control, (III), (IV) and (V) groups rats after 7 and 14 days of diabetes.

Groups	Period treatments	Glucose mg/dl	Triglyceride mg/dl	Total cholesterol mg/dl
		Mean ± SD	Mean ± SD	Mean ± SD
Group I	0 week	129.00 ± 16.18	122.14 ± 8.30	75.92 ± 8.48
	1 week	130.94 ± 11.15	121.22 ± 5.16	73.16 ± 4.54
	2 weeks	132.02 ± 9.36	119.38 ± 4.97	74.46 ± 3.69
	Total	**130.65 ± 12.23 c**	**120.91 ± 6.14 b**	**74.51 ± 5.63 a**
Group II	0 week	126.46 ± 13.73	120.00 ± 14.16	83.86 ± 5.71
	1 week	337.68 ± 23.21	163.69 ± 11.81	72.49 ± 3.86
	2 weeks	339.36 ± 19.07	98.88 ± 5.62	69.62 ± 2.70
	Total	**267.83 ± 104.97 a**	**127.52 ± 29.78 a**	**75.32 ± 7.50 a**
Group III	0 week	129.06 ± 5.86	118.72 ± 10.18	59.56 ± 4.75
	1 week	131.78 ± 5.43	112.94 ± 7.62	67.24 ± 2.75
	2 weeks	133.84 ± 6.15	120.14 ± 10.81	68.98 ± 1.48
	Total	**131.90 ± 5.81 c**	**117.26 ± 9.53 b**	**65.26 ± 5.21b**
Group IV	0 week	119.22 ± 12.93	122.36 ± 6.75	76.76 ± 8.17
	1 week	254.20 ± 19.95	165.12 ± 11.13	72.64 ± 1.93
	2 weeks	192.82 ± 17.67	113.64 ± 8.24	66.25 ± 2.91
	Total	**188.74 ± 16.8 b**	**134.5 ± 8.70 a**	**71.89 ± 6.52 a**
Group V	0 week	138.14 ± 27.56	115.14 ± 3.46	76.40 ± 9.56
	1 week	259.31 ± 28.26	149.93 ± 6.26	73.36 ± 5.26
	2 weeks	224.19 ± 12.97	128.08 ± 4.16	76.52 ± 5.23
	Total	**207.21 ± 22.93 b**	**130.05 ± 4.62 a**	**75.43 ± 6.64 a**

Values are expressed as mean ± SD. Different letters horizontally (a, b, c) indicate that the means are different significantly at P≤0.05. (a= High significant difference, b= significant difference, c= No significant difference).

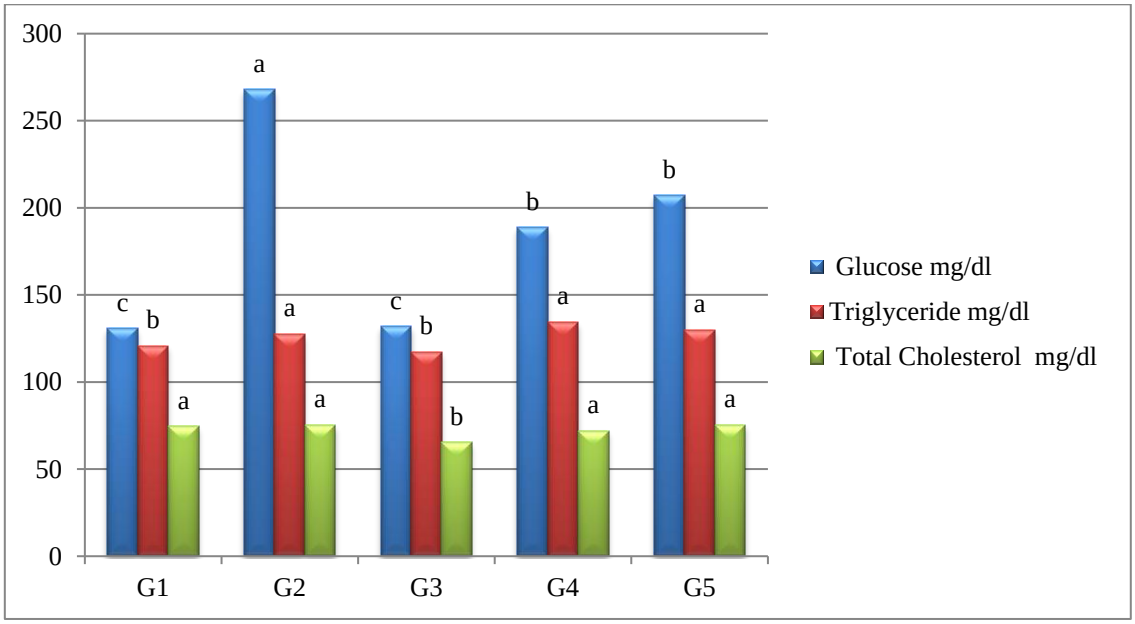

Fig. 1: Mean level values of glucose, triglyceride and total cholesterol for experimental animal groups.

(Table 2) and Fig. (2) displays the effects of Co-administration of the antibiotic AMC along with metformin on electrolytes (Cl^-, Na^+ and K^+) in rats with diabetic mellitus during the course of the two-week treatment period. The findings showed that potassium (K^+) and chloride (Cl^-) do not differ significantly among groups. However, sodium ion (Na^+) in the III, IV, V groups decreased significantly 182.82±6.67, 191.20±14.90, 183.51±11.76 ($P \leq 0.05$) respectively compared with that of II group, likewise, decreased significantly compared with that of I group.

Table 2: Serum electrolytes (Cl^-, Na^+, K^+) in negative and positive control, (III), (IV) and (V) group's rats after 7 and 14 days of diabetes.

Groups	Period Treatments	Cl^- mmol/L	Na^+ mmol/L	K^+ mmol/L
		Mean ± SD	Mean ± SD	Mean ± SD
Group I	0 week	76.50 ± 3.35	195.20 ± 14.87	6.81 ± 0.55
	1 week	74.64 ± 3.59	189.80 ± 15.82	4.56 ± 0.44
	2 weeks	74.40 ± 3.10	190.18 ± 12.03	5.22 ± 0.54
	Total	**75.18 ± 3.25 [a]**	**191.73 ± 13.51[b]**	**5.53 ± 1.09 [a]**
Group II	0 week	74.81 ± 1.24	264.46 ± 14.77	6.77 ± 0.45
	1 week	84.48 ± 2.45	189.02 ± 4.18	4.78 ± 0.66
	2 weeks	76.78 ± 1.78	161.34 ± 4.46	3.88 ± 0.26
	Total	**78.69 ± 4.66 [a]**	**204.94 ± 45.91[a]**	**5.14 ± 1.33 [a]**
Group III	0 week	75.70 ± 1.23	181.20 ± 8.11	6.46 ± 0.51
	1 week	77.58 ± 3.49	185.13 ± 5.29	4.76 ± 0.49
	2 weeks	75.04 ± 1.47	179.15 ± 6.63	4.90 ± 0.50
	Total	**76.11 ± 2.40 [a]**	**182.82 ± 6.67 [c]**	**5.37 ± 0.92 [a]**
Group IV	0 week	77.70 ± 2.26	205.16 ± 18.19	7.36 ± 0.11
	1 week	84.14 ± 2.75	193.32 ± 15.05	4.92 ± 0.53
	2 weeks	77.32 ± 1.49	175.12 ± 11.48	4.56 ± 0.51
	Total	**79.72 ± 3.84 [a]**	**191.20 ± 14.90[c]**	**5.61 ± 1.35 [a]**
Group V	0 week	73.47 ± 1.55	184.26 ± 12.51	6.96 ± 0.52
	1 week	82.14 ± 2.51	176.75 ± 10.74	5.74 ± 0.50
	2 weeks	72.26 ± 2.26	189.52 ± 12.04	5.22 ± 0.22
	Total	**75.96 ± 4.97 [a]**	**183.51 ± 11.76 [c]**	**5.97 ± 0.86 [a]**

Values are expressed as mean ±SD. Different letters horizontally (a, b, c) indicate that the means are different significantly at $P \leq 0.05$. (a= High significant difference, b= Significant difference, c= No significant difference).

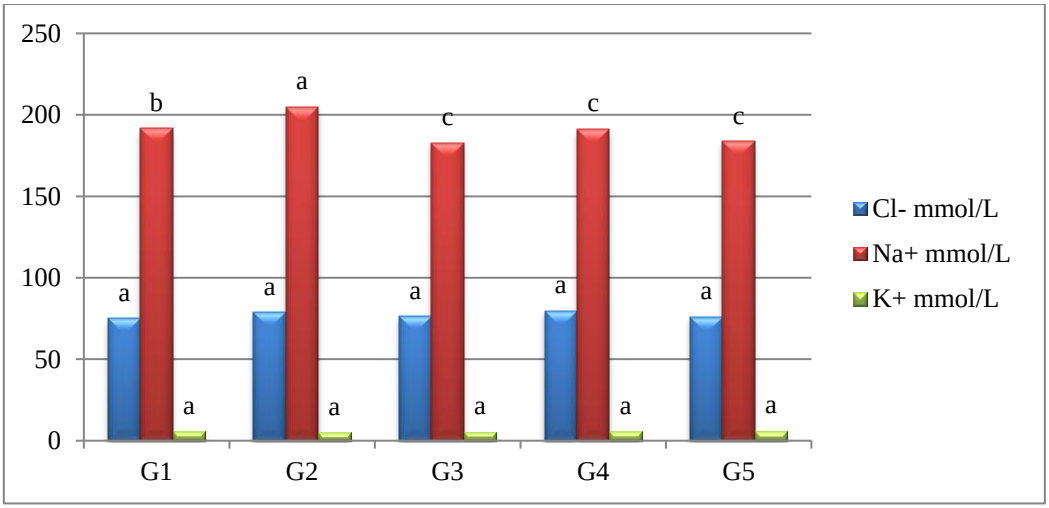

Fig. 2: Mean level values of chloride, sodium and potassium for experimental animal groups.

DISCUSSION

Hyperglycemia determined the presence of diabetes in the rats during the two weeks after alloxan administration. Since these alterations may be totally reversed by insulin therapy, it is likely that they are specific to the diabetic situation in this strictly insulin-dependent example of experimental diabetes (Cooper, 2001). Alloxan is the most frequently used agent to chemically induce T1DM in animals, and it is toxic to pancreatic islet β cells, which can consequently induce hyperglycemia within a few days. The dose required for inducing diabetes by this drug depends on the animal species, route of administration, and nutritional status (Singh *et al*., 2024).

The single IP dose of aloxane (200 mg/kg) successfully enhanced diabetes, and a second dose was given after two weeks to determine whether the antibiotic AMC with metformin might prevent it. In other words, to ensure the survival of the injury (Hasheminasabgorji and Jha, 2021). This fact implies that, reactive oxygen species (ROS) produced by the xanthine oxidase system have a minimal role in alloxan's ability to cause diabetes, and differs with the conclusion reached by (Volpe *et al.*, 2018). Researcher Mistry *et al.* (2023) found that treating diabetic rats developed with alloxan with an ethanolic extracts of mango peel and mangiferin significantly improved the overhead impact due to diabetes at significant ($p \leq 0.05$) and appear to have antidiabetic, glycogenis and antihyperlipidemic actions on diabetic rats produced by alloxan (Arabnozari *et al*., 2024). Demonstrates the significant effectiveness of *Polygonum hyrcanicum* extract in reducing blood glucose levels and diabetic nephropathy it should be noted, the hydroalcoholic extract demonstrates favorable effects on lipid peroxidation. While, (Alou *et al.*, 2024) reviewed a comparative study between cefditoren versus amoxicillin/clavulanic acid for mild diabetic-related foot infections (DFI) with a range of isolated bacteria and came up with emphasizing its microbiological adequacy for empirical treatment of DFI.

On the diabetic rat, the effects of metformin and AMC co-administration were investigated. The diabetic control models valued to support the similar response predicted when the medications are employed in the treatment of DM, while the normal control rat model assisted to swiftly discover the interactions (Arsand *et al*., 2012). Increased blood glucose induces oxidative stress through various distinct pathways. Overall, diabetes leads to the generation of free radicals and oxidative stress, resulting in lipid, protein, and DNA oxidation (Arabnozari *et al*., 2024). (Table 1) shows that the blood glucose and triglyceride levels of the diabetes and diabetic treated groups significantly differed over the treatment period. Since antibiotics make it difficult for sugar to enter cells for use as energy and that would indicate that the causes may be insulin resistance, the blood sugar level may continue to rise when therapy is being administered. While metformin increases the tissue's sensitivity to insulin (Solymár *et al*., 2018).

A decrease in lipoprotein lipase activity and insulin resistance are two of the many causes of elevated triglyceride levels. Studies showed a connection between cells resistant to insulin and the amounts of free fatty acids in blood that are converted to TG in the liver, muscle and heart (Kane *et al*., 2021). Total cholesterol results show that the concentration in the various treatment groups IV, V, and positive were unaffected and this finding is consistent with other observations made earlier. It is possible that metformin and metformin in combination with AMC cause an increase in the body's response to insulin and an inhibition of glycogenolysis in the liver (Yin *et al.*, 2018). The value of blood chloride Cl^-, however, did not substantially alter between diabetic and control animals following AMC and metformin treatments of animals with induced diabetes mellitus, according to the results of this action's testing of Cl^-, Na^+, and K^+ electrolytes. In contrast, the positive group not receiving treatment saw a considerable rise in serum sodium Na^+. This outcome conflicts with previous research by (Ayaz *et al.*, 2023), but agrees with (Palmer and Clegg, 2015). Although references to a clinically relevant decrease in total body water are made, excess or normal plasma sodium concentrations with hyperglycemia. Compared to the negative group, diabetic rats treated with metformin and metformin plus AMC have restored serum electrolyte Na^+ levels to normal. Insulin deficit, which is greater, is a significant worker in the clear impact of potassium

from the cell, thus potassium K^+ was unaffected. In people with type 2 diabetes, the insulin-mediated absorption of glucose is reduced, while the cellular absorption of potassium remains normal. This is due to a change in the intracellular pathways that control the insulin receptor's activation (Khan *et al*., 2019; Datchinamoorthi *et al*., 2016).

limitations in my study are that it requires more time than two weeks to check the biochemical parameters, determine how they influence pancreatic tissue (histological analysis) and the sample size for each group is small. Additionally, it is necessary to examine the variables of other tissues, particularly the liver, for the same medication combination.

CONCLUSIONS

This study concluded that the metformin glucose depletion procedure could be accelerated by co-administration with the antibiotic amoxicillin/clavulanate. This has been observed through the results of low blood sugar and sodium levels of animals caused by diabetes with alloxan and their treatment with a combination of metformin and antibiotics. While, cholesterol, triglycerides, chloride and potassium were also not affected.

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الميتفورمين والأموكسيسيلين/ كلافيونيلات كمزيج مشترك لعلاج ارتفاع سكر الدم في إناث الفئران المستحدث بالألوكسان

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الملخص

يعتبر مرض السكري او ارتفاع السكر في الدم الاسرع والأوسع انتشاراً في العالم. هدفت هذه الدراسة الى فحص تأثير مزيج من الميتفورمين مع المضاد الحيوي الاموكسيلين/ الكلافيونيلات في الجرذان الاناث المستحدث بها مرض السكري بواسطة الالوكسان. قسمت الجرذان المستخدمة في هذه الدراسة الى خمس مجاميع لكل مجموعة خمس حيوانات، أعطيت مجموعة السيطرة (الاولى) الماء والوجبات الغذائية بدون أية معاملة. أما المجموعة الثانية (مجموعة الاصابة) حقنت بجرعة 200 ملغم/كلغم من مادة الالوكسان احادي التميئ في الغشاء البريتوني، في حين المجموعة الثالثة تم اعطائها جرعة 625 ملغ/كلغم من المضاد الحيوي فموياً. أما المجموعة الرابعة أعطيت الميتفورمين بجرعة 500 ملغ/ كغم مع الالوكسان، والمجموعة الخامسة أعطيت المضاد الحيوي زائداً الميتفورمين مع الالوكسان وكانت فترة المعاملة لمدة اربعة عشر يوماً. تم سحب دم من الحيوانات بداية التجربة وبعد 7 ايام وبعد 14 يوم وقيست المتغيرات التالية (كلوكوز الدم، الكوليسترول الكلي، الدهون الثلاثية) اضافة الى الالكتروليتات (كلورايد، صوديوم والبوتاسيوم). كانت النتائج بعدم وجود فروقات معنوية عند مستوى الاحتمالية (اقل من 0.05) للكوليسترول، الدهون الثلاثية، الكلورايد والبوتاسيوم عند المقارنة مع مجموعة السيطرة ومجموعة الإصابة، في حين لوحظت فروقات معنوية عند مستوى الاحتمالية (اقل من 0.05) في الكلوكوز والصوديوم. استنتجت هذه الدراسة إلى أنه يمكن تسريع إجراء استنفاد الميتفورمين للجلوكوز من خلال المزج المشترك مع المضاد الحيوي الاموكسيلين/ الكلافيونيلات. وقد لوحظ ذلك من خلال نتائج انخفاض مستويات السكر في الدم والصوديوم للحيوانات التي يسببها مرض السكري مع الالوكسان وعلاجها مع مزيج من الميتفورمين والمضادات الحيوية. الكوليسترول والدهون الثلاثية والكلوريد والبوتاسيوم لم تتأثر أيضًا.

الكلمات الدالة: داء السكري، ارتفاع سكر الدم، اموكسسيلين/ كلافيونيلات، ميتفورمين، الوكسان.