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Effect of zolmitriptan on blood pressure-relevant cardiovascular biomarkers in rats with experimentally induced hypertension

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Rojgar H. Ali [1]*

Abstract

Background and objective: Zolmitriptan is among widely used medicines for the management of migraine attach, zolmitriptan is acting through stimulating serotonin (5-HT1B/1D) receptors that will cause cranial vasoconstriction. This study was aimed to compare and evaluate the impact of zolmitriptan on the relevant cardiovascular and renal biomarkers during hypertension in rats with experimentally induced hypertension.

Methods: Twenty-four Wister albino male rats were randomly divided into four groups of six rats each. The first group (Group I) of rats served as the control group. To induce hypertension, the rats in the second (Group II), third (Group III) and fourth (Group IV) groups have received an intraperitoneal injection of cadmium chloride CdCl2 a dose of 1.5 mg/kg/day for 14 days. The rats in Group II were considered as the positive control. Whereas, rats in Group III received zolmitriptan orally (2 mg/kg/day), and Group IV rats received nifedipine dose of 10mg/kg for two weeks concurrently with $CdCl_2$.

Results: Inducing hypertension with CdCl2 injection significantly increased the systolic, diastolic, and mean blood pressure in Group II compared with Group I, respectively. The systolic, diastolic, and mean blood pressure in rats that received zolmitriptan did not exhibit any statistically significant differences from the rats in Group II, whereas nifedipine has significantly reduced blood pressure in group IV rats.

Intraperitoneal injection of $CdCl_2$ increased the concentrations of endothelin and nitric oxide as well as renin activity level in hypertensive Group II rats compared to control rats. Zolmitriptan administration did not produce any significant change in the endothelin and nitric oxide levels.

Inducing hypertension in rats significantly reduced the corticosterone level. In contrast, administering medications in Group III and VI rats did not produce any statistically significant change in the serum concentration of corticosterone.

Conclusion: Zolmitriptan administration (2 mg/kg/day, p.o) showed no statistically significant effects on the systolic, diastolic, and mean blood pressure in rats with experimentally induced hypertension. Zolmitriptan has also failed to produce any statistically significant change in the levels of endothelin-1, renin, nitric oxide, corticosterone, and serum creatinine in rats with hypertension.

Keywords: Zolmitriptan; Blood pressure; Hypertension; Nitric oxide; Endothelin-1.

Introduction

Zolmitriptan is used to treat symptoms of migraine, it belongs to a class of medications calledtriptans, members of this medication class are indicated as an essential choice of treatment in acute migraine episodes that acts through stimulating serotonin (5-HT1B/1D) receptors that will lead to vasoconstriction in the brain, which is considered to be the triggering cause of migraine.[1]

The first member of triptans is sumatriptan and it was followed by development of newer generations of triptans that act as

[1] Department of Pharmacology and Toxicology, College of Pharmacy, Hawler Medical University, Erbil, Iraq.
Correspondence: rojgar.hamed@hmu.edu.krd

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agonists on 5-HT1B/1D receptors as well, including zolmitriptan.[2]

There are several possible mechanisms by which zolmitriptan relieves symptoms of migraine, the first of which is vasoconstriction of dilated blood vessels in brain, restricting neurogenic inflammation around blood vessels, and inhibiting neuronal firing within trigeminal vascular system.[3] When this compound interacts with 5-HT1D receptors it blocks the release of certain vasoactive neuropeptides by inhibiting trigeminal nerve activation and inhibit the transmission of nociceptive signals to the brain.[4]

Among the attributed actions of zolmitriptan, it inhibits the release of vasoactive peptides, including substance P, a CGR peptide; thus, zolmitriptan is expected to affect the vascular function.[5]

This study was aimed to compare and evaluate the impact of zolmitriptanon the relevant cardiovascular and renal biomarkers during hypertension in rats with experimentally induced hypertension.

Methods

Drugs:

Zolmitriptan, nifedipine, cadmium chloride, saline.

Animals:

Twenty-four male four-month-old Wister albino rats weighing between 200 and 250 g were used in this study. The animals had free access to water and standard rat food pellets and were kept in the animal house of the Hawler Medical University. The temperature of the animal chambers was kept at 25°C with a 12/12 dark/light cycle.

Materials:

Endothelin-1, nitric oxide, corticosterone, and renin ELISA rat kits were purchased from Elabsciences (Houston-Texas, USA).

Cadmium chloride ($CdCl_2$) was purchased from Sigma-Aldrich (Burlington, MA, United States), and the zolmitriptan 2.5mg tablet and nifedipine 20mg were purchased in a pharmacy in Erbil city/Iraq manufactured by Actavis (Devonshire, UK) and Cipla pharmaceuticals (Mumbai, India) respectively.

Study design:

Twenty-four Wister albino male rats were randomly divided into four groups of six rats each. The first group (Group I) of rats served as the control group. To induce hypertension, the rats in the second (Group II), third (Group III) and fourth (Group IV) groups, have received an intraperitoneal injection of cadmium chloride CdCl2a dose of 1.5 mg/kg/day for 14 days.[6]

The rats in Group II were considered as the positive control. Whereas rats in Group III received zolmitriptan orally (2 mg/kg/ day),[7] and Group IV rats received nifedipine dose of 10mg/kg[7] for two weeks concurrently with $CdCl_2$.

The systolic, diastolic, and heart rate were recorded at the day 14th using CODA multi-channel non-invasive blood pressure system.

On Day 14th, rats were anaesthetized with10 mg/kg of xylazine and 125 mg/kg of ketamine through an intraperitoneal injection.[9] Blood samples were taken from each rat though cardiac puncturing and were centrifuged at 3000rpm for 15 minutes then the produced serum was analyzed for different biomarkers.

In addition, at the end of the experiment, animals were euthanized through cervical dislocation. The death of the animals was verified through the absence of a corneal reflex, failure to detect respiration, and absence of a heartbeat. For the blinded investigator, the samples were coded with random letters. The true identity of the samples was only revealed after all samples were analysed.

The study has been authorized by the ethics committee of the Hawler Medical University College of Pharmacy, 83 with the permission number HMU-PE 25092021 -401. During practice we followed "Guide for the Care and Use of Laboratory Animals," which was developed by the National Academy of Science and published by the National Institute of Health.

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Biochemical assays:

Plasma endothelin, renin, nitric oxide, and corticosterone were measured in the central laboratory centre of Erbil directorate of health using ELISA kits for rats. The serum creatinine, blood urea nitrogen, serum ions, and lipid profile parameters were measured using specific reagents for each parameter through the Cobas-Roche analyser.

Statistical analysis

All data were expressed as ± standard error mean. The results were evaluated using the statistical package for social sciences (SPSS, version 23)., and the differences in all parameters of the controlled and medicated rats were analysed using a one-way analysis of variance. The groups were compared using the Tukey test, and a change was considered statistically significant when P <0.05.

Results

Table 1 presents the results, revealing that the $CdCl_2$ injection significantly increased the systolic, diastolic, and mean blood pressure in Group II (138 ± 2, 94 ± 2.1, 108.6 ± 1.4) compared with Group I (116.1 ± 4.9, 81.6 ± 3.38, 93.1 ± 93.7), respectively. The systolic, diastolic, and mean blood pressure in rats that received zolmitriptan did not exhibit any statistically significant differences from the rats in Group II, whereas the rats that received nifedipine experienced a significant reduction in blood pressure compared with the rats in Group II. This significant reduction resulted in a normal blood pressure state in Group IV rats.

Table 1 Effects of zolmitriptan (2 mg/kg, oral) and nifedipine (10 mg.kg, oral) on arterial blood pressure and heart rate: systolic blood pressure, diastolic blood pressure, mean blood pressure, and heart rate

	Control group	Positive control?	Zolmitriptan group	Nifedipine group	*P*(ANOVA)
Systolic BP	116.1 ±4.9 a	138 ±2 b	139.6 ±1.14 b	119.8 ±2.57 a	0.0001*
Diastolic BP	81.6 ±3.38 a	94 ±2.1 b	92.8 ±2 b	81.5 ±2.1 a	0.001*
Mean BP	93.1 ±93.7 a	108.6 ±1.4 b	108.4 ±1.45 b	94.2 ±1.08 a	0.0001*
Heart rate	300.6 ±12.7 a	277.3 ±17.25 a	298.6 ±21.6 a	291.5 ±7.9 a	0.740

Values are expressed as mean ± SEM
Means denoted by a different letter indicates significant differences between groups (P <0.05).

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The results in Table 2 reveal that the intraperitoneal injection of $CdCl_2$ increased the concentrations of endothelin and nitric oxide from 1.55 ± 0.14 µmol/L to 5.95 ± 0.66 pg/mL in hypertensive rats compared to control rats (4.71 ±0.45 µmol/L, 17.26 ±1.54 pg/mL). Zolmitriptan administration did not produce any significant change in the endothelin and nitric oxide levels, whereas nifedipine induced a further increase in the levels of both parameters. The increase was statistically significant for rats in the positive control group.

Inducing hypertension in rats significantly reduced the corticosterone level from 6.1 ± 0.62 ng/mL to 2.95 ±0.64 ng/mL. In contrast, administering medications in Group III and VI rats did not produce any statistically significant change in the serum concentration of corticosterone.

Renin activity increased significantly with induced hypertension, from 434.16 ± 21 pg/mL to 631.5 ± 39.3 pg/ml. Administering zolmitriptan did not produce any significant change in renin activity. However, administering nifedipine to rats with hypertension significantly reduced renin activity. Serum creatinine increased significantly with induced hypertension, from 0.76 mg/dl to 1.53 mg/dl. The rats that received zolmitriptan did not exhibit a significant change in circulating creatinine level compared to Group II, whereas administering nifedipine statistically significantly reduced the creatinine level.

Table 2 Effects of zolmitriptan (2 mg/kg, oral) and nifedipine (10 mg.kg, oral) on cardiovascular and renal biomarkers: Endothelin-1, Nitric oxide, Corticosterone, renin, serum creatinine, and blood urea nitrogen.

	Control group?	Positive control?	Zolmitriptan group	Nifedipine group	*P* (ANOVA)
Endothelin-1 pg/ml	1.55 ±.0.14 a	4.71 ±0.45 b	4.7 ±0.5 b	3.06 ±0.31 a	0.0001*
Nitric oxide µmole/litre	5.95 ±0.66 a	17.26 ±1.54 b	11.98 ±1.23 b	23.7 ±2.11 c	0.0001*
Corticosterone ng/mL	5.76 ±0.43 a	6.3 ±0.76 a	6.03 ±0.77 a	5.81 ±0.45 a	0.001*
Renin pg/ml	434.16 ±21 a	631.5 ±39.3 bc	686.6 ±40.7 c	535.5 ±20.4 ab	0.0001*
serum Creatinine mg/ dl	0.76 ±0.16 ab	1.53 ±0.18 c	1.35 ±0.1 bc	1.09 ±.1.1 a	0.002*
BUN mg/dl	15.03 ±2.2 a	18.25 ±1.1 a	19.16 ±1.1 a	15.58.1.27 a	0.184

Values are expressed as mean ± SEM
Means denoted by a different letter indicates significant differences between groups (*P* <0.05).

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Discussion

Because the impact of zolmitriptan on blood pressure is mild but kind of controversial, as it's been shown that single doses of zolmitriptan 1 to 50mg produce increases in blood pressure but not significant, and individual data often showed high variability. However, precautions for the use of zolmitriptan states that zolmitriptan can raise blood pressure to dangerous levels.

This study was aimed to find out if high dose of zolmitriptan has any significant effect on blood pressure or not in samples with experimentally induced hypertension.[10]

Results reveal that $CdCl_2$ successfully induced hypertension in experimental rats. This property of $CdCl_2$ is attributed to its ability to increase arterial stiffness, enhancing oxidative stress and vascular remodeling.[11]

Nitric oxide and endothelin significantly increased in group II rats, in response to increased blood pressure, resulting from nitric oxide synthase activation aiming to lower increased blood pressure.[12]

Administering nifedipine reduced nitric oxide and endothelin levels significantly compared to rats in positive control group, which is probably due to reducing the workload on the vascular wall by blocking calcium channels responsible for feeding muscle contraction.

Although zolmitriptan reduces many circulating vasoactive peptides,[5] it has failsto demonstrate statistically significant change in the endothelin and nitric oxide levels in rats with hypertension.

Corticosterone, the most abundant circulating steroid in rats, did not show any significant change between different groups, although it's increased in positive control group due to the stress produced by $CdCl_2$,[13] however, the increase was not statistically significant.

Renin activity was evaluated in all groups to assess the influence of zolmitriptan on the renin-angiotensin-aldosterone system (RAAS). Inducing hypertension with $CdCl_2$ significantly increased the renin level in circulation, enhancing aldosterone secretion and water-sodium reabsorption. This outcome illustrates one of the mechanisms behind the ability of $CdCl_2$ to induce hypertension.

The results indicate that zolmitriptan failed to demonstrate statistically significant changes in the circulating renin level in Group III compared to Group II. The inhibitory effects of zolmitriptan on vasoactive peptides[5] appeared to be mild regarding imparting any effect on the RAAS. Its lack of effect on the RAAS could explain its insignificant effect on the circulating creatinine and blood urea nitrogen (renal function).

Although zolmitriptan produced a slight increase in blood pressure, as presented in the table, it failed to significantly change the systolic, diastolic, and mean blood pressure levels. These results disagree with the results shown by Jamieson who stated that triptans have a significant transient increase in blood pressure,[14] the results agree with those of a study in which three randomised trials with different triptans, including zolmitriptan, revealed that triptan use has no significant influence on blood pressure.[14]

Conclusion

The oral administration of zolmitriptan (2 mg/kg/day) to hypertensive rats has no statistically significant effect on the systolic, diastolic, and mean blood pressure in rats with experimentally induced hypertension. Oral zolmitriptan also failed to produce any statistically significant change in the endothelin-1, renin, nitric oxide, corticosterone, and serum creatinine levels in rats with hypertension.

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Competing interests

The author declares that he has no competing interests.

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