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Original Research Article

HYPOLIPIDEMIC EFFECT OF RANOLAZINE IN STREPTOZOTOCIN-INDUCED DIABETIC RATS: AN EXPERIMENTAL STUDY

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ABSTRACT

Background: Dyslipidaemia is an important metabolic abnormality associated with diabetes and contributes to atherosclerotic cardiovascular disease. Ranolazine is an established antianginal drug, and previous experimental and clinical observations have suggested potentially favourable metabolic effects. The present study was undertaken to evaluate specifically the hypolipidemic effect of ranolazine in streptozotocin-induced diabetic adult male albino rats, without considering its antihyperglycaemic effects. **Materials and Methods:** Twenty-four adult male albino rats weighing 150–200 g were allocated into four groups of six animals each: control, standard, ranolazine 45 mg/kg and ranolazine 90 mg/kg. Diabetes was induced using streptozotocin according to the study protocol. The control group received normal feed and distilled water, the standard group received glibenclamide 1 mg/kg, and the two test groups received ranolazine 45 mg/kg or 90 mg/kg orally once daily for 28 days. Serum cholesterol was assessed on day 1 and day 28. Group means and standard deviations were calculated, and one-way analysis of variance was used for between-group comparison; change from baseline was also examined. **Results:** Baseline serum cholesterol values were comparable among the four groups (ANOVA, p=0.821). By day 28, mean serum cholesterol increased markedly in the control group from 114.67±4.59 to 216.17±6.43, whereas it decreased in the standard group from 118.00±8.72 to 104.67±5.89, in the ranolazine 45 mg/kg group from 117.33±5.24 to 112.67±4.32, and in the ranolazine 90 mg/kg group from 116.83±6.24 to 109.33±6.50. The corresponding mean changes were +101.50, −13.33, −4.67 and −7.50, respectively. The day-28 between-group difference was highly significant (ANOVA F=506.03, p<0.001), as was the difference in change from baseline (F=1294.30, p<0.001). **Conclusion:** In this experimental model, ranolazine demonstrated a favourable hypolipidemic effect over 28 days, as reflected by lower serum cholesterol compared with untreated diabetic controls. The findings support further investigation of ranolazine and its metabolic effects, particularly in conditions in which diabetes and cardiovascular risk coexist.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder associated with substantial cardiovascular morbidity and mortality. Cardiovascular disease is a major cause of adverse outcomes in individuals with diabetes, and the relationship is mediated not only by abnormalities of glucose metabolism but also by a broad range of metabolic and vascular disturbances.[1-3] Dyslipidaemia is particularly important because abnormalities in circulating lipids promote lipid accumulation in the vascular wall and contribute to atherosclerosis.[4,5] Diabetes-associated insulin resistance can increase free fatty-acid flux and hepatic triglyceride-rich lipoprotein production, while changes in lipoprotein metabolism may be accompanied by adverse alterations in high-density lipoprotein concentrations.[6,7]

The clinical importance of lipid abnormalities in diabetes is underscored by the close relationship between diabetes and cardiovascular disease. Diabetes is an independent risk factor for atherosclerotic disease, and multifactorial cardiovascular risk reduction includes appropriate management of dyslipidaemia.[7,8] Alterations in major lipid fractions, including cholesterol, triglycerides, low-density lipoprotein and high-density lipoprotein, provide useful information regarding lipid metabolism and may indicate increased susceptibility to atherosclerosis. The

association between diabetes and cardiovascular risk therefore provides a rationale for evaluating pharmacological interventions that may influence metabolic as well as cardiovascular pathways.[9,10]

Ranolazine is a piperazine derivative and an established antianginal agent approved for the treatment of stable angina.[11-13] Its pharmacological profile differs from conventional haemodynamically active antianginal agents, and clinical studies have generated interest in additional metabolic effects. Although the metabolic actions of ranolazine have received attention in the context of diabetic patients with coronary disease, the present article deliberately focuses on its hypolipidemic effect. Experimental evidence has previously suggested that ranolazine may improve lipid homeostasis in streptozotocin-treated albino Wistar rats, with significant reductions in lipid-profile parameters compared with untreated controls.[14]

Because cardiovascular risk in diabetes is closely linked to adverse lipid metabolism, an experimental assessment of ranolazine's effect on serum cholesterol is of potential pharmacological interest. The present study therefore reanalyses the lipid component of the original experimental work and excludes the antihyperglycaemic and insulin-related outcomes. The objective was to evaluate the effect of ranolazine at doses of 45 mg/kg and 90 mg/kg on serum cholesterol in streptozotocin-induced diabetic adult male albino rats over a 28-day treatment period. The primary objective was to evaluate the hypolipidemic effect of ranolazine on serum cholesterol in streptozotocin-induced diabetic adult male albino rats. A secondary objective was to compare the effects of ranolazine at 45 mg/kg and 90 mg/kg with an untreated diabetic control group and a standard-treatment group over 28 days.

MATERIALS AND METHODS

This experimental study was conducted in a tertiary care teaching hospital. The study was conducted according to the principles of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). The study was done for a period of one year

Twenty-four adult male albino rats weighing approximately 150–200 g were used. The animals were divided into four groups of six rats each. Animals were maintained on standard pellet feed and tap water ad libitum and were housed with appropriate identification and routine hygiene. Streptozotocin was used to induce the diabetic experimental model. The source document describes administration after overnight fasting by intraperitoneal injection; the methodological sections report both 50 mg/kg and 45 mg/kg in different passages. To avoid silently reconciling this discrepancy, the present article does not assign a single definitive streptozotocin dose beyond stating that streptozotocin was used according to the original study protocol.

The four groups comprised an untreated control group receiving normal feed and distilled water, a standard group receiving glibenclamide 1 mg/kg orally once daily, a test group receiving ranolazine 45 mg/kg orally once daily, and a second test group receiving ranolazine 90 mg/kg orally once daily. Treatment was continued for 28 days. Ranolazine was administered after preparation of the tablet formulation in distilled water, as described in the original protocol.

For the lipid-focused analysis, serum cholesterol was the outcome measure. Blood samples were collected according to the procedures described in the source study, and serum cholesterol was recorded on day 1 and day 28. The original tables report the cholesterol unit as mg/kg; this unit has been retained in the present article to preserve fidelity to the source data. No antihyperglycaemic, glucose, insulin, or other metabolic outcome has been included in the analysis. Continuous variables were summarized as mean ± sd. Baseline comparability among groups was evaluated using one-way analysis of variance. Day-28 cholesterol values were compared between groups using one-way ANOVA, and the change from baseline was calculated for each animal and compared among groups. The source thesis also reports use of Bonferroni post-hoc testing; however, exact pairwise post-hoc p-values were not provided in the supplied document. Therefore, this article reports the reproducible omnibus ANOVA results calculated from the supplied individual-level cholesterol data and does not invent pairwise p-values.

RESULTS

Twenty-four rats were included in the lipid analysis, with six animals in each of the four study groups. Individual serum cholesterol values were available for day 1 and day 28. At baseline, mean serum cholesterol ranged from 114.67±4.59 in the control group to 118.00±8.72 in the standard group. The 45 mg/kg and 90 mg/kg ranolazine groups had baseline means of 117.33±5.24 and 116.83±6.24, respectively. One-way ANOVA demonstrated no statistically significant difference among groups at baseline ($F=0.305$, $p=0.821$), indicating satisfactory baseline comparability.

Table 1: Baseline serum cholesterol (day 1)

Group	n	Mean ± SD	Range
Control	6	114.67 ± 4.59	109–120
Standard	6	118.00 ± 8.72	106–129
Ranolazine 45 mg/kg	6	117.33 ± 5.24	111–125
Ranolazine 90 mg/kg	6	116.83 ± 6.24	109–125

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On day 28, a marked divergence between the untreated control group and the treated groups was observed. Mean serum cholesterol increased from 114.67±4.59 at baseline to 216.17±6.43 in the control group. In contrast, the standard-treatment group showed a reduction to 104.67±5.89, while the ranolazine 45 mg/kg and 90 mg/kg groups showed reductions to 112.67±4.32 and 109.33±6.50, respectively. Thus, both ranolazine doses were associated with substantially lower day-28 cholesterol than the untreated diabetic control group.

Table 2: Serum cholesterol on day 28

Group	n	Mean ± SD	Range
Control	6	216.17 ± 6.43	209–225
Standard	6	104.67 ± 5.89	95–110
Ranolazine 45 mg/kg	6	112.67 ± 4.32	108–119
Ranolazine 90 mg/kg	6	109.33 ± 6.50	102–119

The magnitude of change from baseline further demonstrated the difference among groups. The control group showed a mean increase of 101.50 units, corresponding to an 88.52% increase from baseline. The standard group showed a mean decrease of 13.33 units (11.30% decrease), while the ranolazine 45 mg/kg and 90 mg/kg groups showed mean decreases of 4.67 units (3.98% decrease) and 7.50 units (6.42% decrease), respectively. Between-group ANOVA for the change from baseline was highly significant ($F=1294.30$, $p<0.001$).

Table 3: Change in serum cholesterol from day 1 to day 28

Group	Baseline mean	Day-28 mean	Mean change
Control	114.67	216.17	101.50
Standard	118.00	104.67	-13.33
Ranolazine 45 mg/kg	117.33	112.67	-4.67
Ranolazine 90 mg/kg	116.83	109.33	-7.50

The day-28 between-group comparison was also highly significant ($F=506.03$, $p<0.001$). The 90 mg/kg ranolazine group produced a numerically greater reduction in mean cholesterol than the 45 mg/kg group, although the supplied thesis does not provide sufficient pairwise post-hoc numerical results to establish statistical superiority of one ranolazine dose over the other. The overall pattern indicates that ranolazine treatment prevented the pronounced increase in serum cholesterol observed in untreated controls.

Table 4: Percentage change in mean serum cholesterol

Group	Day-1 mean	Day-28 mean	% change
Control	114.67	216.17	88.52%
Standard	118.00	104.67	-11.30%
Ranolazine 45 mg/kg	117.33	112.67	-3.98%
Ranolazine 90 mg/kg	116.83	109.33	-6.42%

Table 5: ANOVA summary for serum cholesterol

Analysis	F value	p value	Interpretation
Baseline, day 1	0.305	0.821	No significant baseline difference
Day 28	506.03	<0.001	Highly significant between-group difference
Change from baseline	1294.30	<0.001	Highly significant between-group difference

DISCUSSION

The present analysis demonstrates a favourable effect of ranolazine on serum cholesterol in streptozotocin-induced diabetic rats. The most important observation was not simply the modest fall in cholesterol in the ranolazine-treated groups, but the contrast with the untreated control group. Baseline cholesterol values were closely comparable, whereas after 28 days the control animals demonstrated a substantial rise in mean serum cholesterol. Both ranolazine-treated groups avoided this marked deterioration, with the 90 mg/kg group showing a numerically greater reduction than the 45 mg/kg group. These findings indicate that ranolazine was associated with preservation of a more favourable cholesterol profile during the experimental period.

The biological relevance of this finding lies in the established association between diabetes, dyslipidaemia and cardiovascular disease. Diabetes promotes an atherogenic milieu through abnormalities in fatty-acid handling, lipoprotein production and cholesterol metabolism. Increased free-fatty-acid availability in insulin-resistant states can stimulate hepatic triglyceride and VLDL production and is associated with adverse apolipoprotein and HDL-related changes.[6,7] Dyslipidaemia consequently contributes to lipid deposition in the vascular wall and progression of atherosclerosis.6 The ability of a cardiovascular drug

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to exert a favourable effect on a lipid-related parameter is therefore potentially relevant, although the present animal study cannot establish clinical cardiovascular benefit. The findings are broadly consistent with the earlier experimental study by Bashir and Kalabharathi, which reported that ranolazine improved glucose and lipid homeostasis in streptozotocin-induced diabetes mellitus in albino Wistar rats and described statistically significant reductions in lipid-profile parameters compared with controls.[14] The current analysis isolates the cholesterol component of the supplied experimental dataset and demonstrates the same general direction of effect. The concordance between the two experimental observations strengthens the rationale for further investigation of ranolazine's lipid-related actions. A dose-related pattern was suggested but not conclusively demonstrated statistically. The mean reduction in cholesterol was 4.67 units with 45 mg/kg and 7.50 units with 90 mg/kg, corresponding to reductions of 3.98% and 6.42% from baseline, respectively. However, because the sample size was small and the supplied thesis does not report exact pairwise post-hoc p-values, it would be inappropriate to claim that 90 mg/kg is statistically superior to 45 mg/kg. The appropriate interpretation is that the higher dose produced a numerically greater reduction in this dataset.

The mechanism responsible for the observed lipid effect cannot be established from the present experiment. Ranolazine is primarily recognized as an antianginal drug, and contemporary reviews have described its potential metabolic effects as an area of continuing interest.[13] The original thesis also cites experimental work suggesting broader metabolic actions of ranolazine.[14] Nevertheless, the present study did not measure hepatic lipid synthesis, lipoprotein turnover, lipid oxidation, receptor-mediated pathways, or molecular markers that could distinguish among possible mechanisms. Therefore, mechanistic explanations should remain hypotheses rather than conclusions.

Several limitations should be considered. First, the study included only 24 animals, with six animals per group, which limits statistical precision and generalizability. Second, serum cholesterol was the lipid outcome available in the supplied dataset; triglycerides, LDL cholesterol, HDL cholesterol and other lipid fractions were not presented as individual-level data in the source material and therefore were not reconstructed or inferred. Third, the source document contains an internal discrepancy regarding the streptozotocin dose, reporting 50 mg/kg in one methodological section and 45 mg/kg elsewhere; this was retained as a source limitation rather than silently corrected. Fourth, the study duration was limited to 28 days, and no long-term assessment of lipid effects or cardiovascular outcomes was undertaken. Finally, findings from an experimental diabetic-rat model cannot be directly extrapolated to humans without appropriately designed clinical studies.

CONCLUSION

In this experimental study of streptozotocin-induced diabetic adult male albino rats, ranolazine demonstrated a favourable hypolipidemic effect as assessed by serum cholesterol over 28 days. Baseline cholesterol values were comparable among groups, whereas untreated controls developed a pronounced increase in cholesterol. Both ranolazine doses prevented this rise and produced lower day-28 cholesterol values, with the 90 mg/kg dose showing a numerically greater reduction than the 45 mg/kg dose. However, the small sample size, limited lipid outcome assessment and absence of mechanistic measurements warrant cautious interpretation. Further experimental and clinical studies are required to determine the reproducibility, dose-response relationship, mechanism and clinical relevance of the hypolipidemic effect of ranolazine.

REFERENCES

1. Diabetes Canada Clinical Practice Guidelines Expert Committee, Punthakee Z, Goldenberg R, Katz P. Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome. Can J Diabetes. 2018;42 Suppl 1:S10–S15.
2. International Diabetes Federation. IDF Diabetes Atlas. 8th ed. Brussels, Belgium: International Diabetes Federation; 2017.
3. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract. 2019.
4. Uusitupa M. Lifestyles Matter in the Prevention of Type 2 Diabetes. Diabetes Care. 2002;25:1650–1651.
5. Cole JB, Florez JC. Genetics of diabetes mellitus and diabetes complications. Nat Rev Nephrol. 2020.
6. Matheus ASM, Tannus LRM, Cobas RA, Palma CCSS, Negrato CA, Gomes MB. Impact of diabetes on cardiovascular disease: an update. Int J Hypertens. 2013;2013:653789.
7. Leon BM, Maddox TM. Diabetes and cardiovascular disease: Epidemiology, biological mechanisms, treatment recommendations and future research. World J Diabetes. 2015;6(13):1246–1258.
8. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. Cardiovasc Diabetol. 2018;17(1):83.
9. Rijzewijk LJ, et al. Myocardial steatosis is an independent predictor of diastolic dysfunction in type 2 diabetes mellitus. J Am Coll Cardiol. 2008;52(22):1793–1799.
10. Ganesan K, Rana MBM, Sultan S. Oral Hypoglycemic Medications. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2020.
11. Reddy BM, Weintraub HS, Schwartzbard AZ. Ranolazine. Tex Heart Inst J. 2010;37(6):641–647.
12. Caminiti G, Fossati C, Battaglia D, Massaro R, Rosano G, Volterrani M. Ranolazine improves insulin resistance in non-diabetic patients with coronary heart disease. A pilot study. Int J Cardiol. 2016;219:127–129.
13. Rayner-Hartley E, Sedlak T. Ranolazine: A Contemporary Review. J Am Heart Assoc. 2016;5(3):e003196.
-metabolic effects of ranolazine. A truly multifaceted drug? J Cardiol Ther. 2018;5(1):742–746.
14. Bashir S, Kalabharathi HL. Ranolazine improves glucose and lipid homeostasis in streptozotocin induced diabetes mellitus in albino Wistar rats. Int J Basic Clin Pharmacol. 2017;5(4):1477–1480.

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