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The effect of bempedoic acid an ATP-citrate lyase inhibitor on cardiovascular risk factors in rats with experimentally induced myocardial infarction and hyperlipidemia

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ABSTRACT

Control of hyperlipidemia is believed to reduce major cardiovascular events such as cardiovascular death, myocardial infarction, nonfatal stroke, hospitalization for unstable angina, and coronary revascularization. The benefits of monotherapy with Bempedoic acid (BA) as a hypolipidemic agent given after induction of myocardial infarction (MI) in reducing the risk of acute MI worth being investigated, therefore this study was designed to investigate the effectiveness of Bempedoic acid on reducing cardiovascular risk factors in rats with induced hyperlipidemia and myocardial infarction compared to Rosuvastatin. Male albino rats (n=40) were divided into five equal groups, each with eight rats, the first group served as a negative control group, the second group (diet-induced hyperlipidemia and Isoprenaline induced myocardial infarction) served as a positive control group, the third group (diet-induced hyperlipidemia and Isoprenaline induced myocardial infarction) received daily oral administration of Rosuvastatin for 12 weeks, the fourth group (diet-induced hyperlipidemia, DIH) received Bempedoic acid for 4 weeks as prophylaxis and then myocardial infarction was induced and Bempedoic acid administration was continued for the remaining 8 weeks, and the fifth group (diet-induced hyperlipidemia and Isoprenaline induced myocardial infarction) received a daily oral administration of Bempedoic acid for 12 weeks as a treatment. After 12 weeks, blood samples were withdrawn by cardiac puncture for measuring and evaluating lipid profiles and other parameters. Bempedoic acid and Rosuvastatin significantly reduce mean serum levels of lipid profiles; Total cholesterol, LDL and triglyceride, increase HDL and reduce cardiac enzyme levels as compared with the positive control group. The findings from this study suggested that Bempedoic acid as monotherapy either as a therapy or as prophylaxis was effective in reducing lipid parameters, LDL, Tch, and TG and cardiac enzymes creatine kinase-MB (CK-MB) and serum level of cardiac troponin-I (cTn-I) compared with the positive control group and was not superior to Rosuvastatin in these parameters but taking BA as prophylaxis could prevent the morbidity with cardiovascular events as it was effective in reducing the above parameters by greater percentages than BA and Rosuvastatin therapy. Both drugs showed similar profiles in blood pressure and heart rate measurements.

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Introduction

Hyperlipidemia is a major modifiable risk factor for the development of atherosclerotic cardiovascular disease (ASCVD). Clinical trials have shown that lowering the low-density lipoprotein cholesterol (LDL-C) level is the corner stone for the secondary prevention of ASCVD events, especially among patients with acute myocardial infarction MI (1). Particularly in the Western Hemisphere but also globally, hyperlipidemia is quite prevalent. According to current estimates, there are 28.5 million persons in the adult population (those who are 20 years of age and older) who have elevated levels of total serum cholesterol, with a prevalence rate of 11.9% (2). One of the difficulties in the management of hyperlipidemia is treatment resistance. Statins with their pleiotropic effects have proven efficacy for the primary and secondary prevention of cardiovascular disease. This recommendation is based on clinical trials that showed lowering LDL levels by statins following MI was associated with a significant reduction in myocardial Ischemia and risks of major adverse cardiovascular events (3). However, many patients with familial hypercholesterolemia, or with cardiovascular risk factors remains suboptimal to attain the target LDL goal, and in some cases, patients may be unable to tolerate effective doses of statins due to adverse effects, such as muscle pain (4). This necessitates an alternative lipid-lowering agent with high efficacy and safety profile.

Bempedoic acid (BA) is a new hypolipidemic agent approved by the FDA in 2020 for the treatment of adults who require additional low-density lipoprotein-cholesterol lowering and recommended by the European Medicines Agency (EMA) to treat adults with primary hypercholesterolemia and mixed dyslipidemia (5, 6). Bempedoic acid inhibits cholesterol synthesis through the inhibition of adenosine triphosphate citrate lyase (ACL) an enzyme that lies two steps upstream of HMG-CoA Reductase resulting in increased expression of LDL receptors (7). This different pathway would lead to better efficacy and may be the reason behind the lack of muscle-related adverse effects seen with this agent (8). Bempedoic

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acid is a prodrug, given orally once daily, which must be activated by the very long-chain acyl-CoA synthetase 1 in the liver, which is lacking in the majority of peripheral tissues (9). The benefits of monotherapy with Bempedoic acid as a hypolipidemic agent given after myocardial infarction (MI) or prophylactically pre-MI in reducing the risk of acute MI is noteworthy, therefore the present study aimed to investigate the effects of post-isoprenaline-induced MI treatment with BA compared to Rosuvastatin, or prophylactic administration of BA prior to isoprenaline-induced MI in rats, by assessing the markers of lipid profile and cardiac damage, serum activity of creatine kinase-MB (CK-MB) and serum level of cardiac troponin-I (cTn-I), in addition to blood pressure monitoring (Systolic, Diastolic, and heart rate).

Materials and Methods

Animals

Forty male rats of albino type, weights were (180-300) g, 6-7 months old were utilized in this study. The experiment was done in the animal house laboratory at the college of pharmacy, Hawler Medical University from October 2021 to May 2022. The rats were kept under hygienic conditions and the health situation at a controlled temperature of 20-22°C with a half day of dark and a half day of the light cycle. During the experiment, the rats were afforded easy access to water and a solid pellet diet.

Materials

Bempedoic acid 180mg (Daiichi-Sankyo, Germany) was purchased from Germany and Rosuvastatin 20mg (Crestor) was bought at the pharmacy. Isoprenaline for inducting myocardial infarction was purchased from Glentham LIFE SCIENCES, CAS 51-30-9, United Kingdom. Ketamine 10% supplied by (Dutch Farm, Netherlands) and xylazine supplied by (Interchemie, Netherlands) were used for anesthetizing the rats. Systolic and diastolic blood pressure along with heart rates were measured non-invasively in all rats before and after drug administration. Blood pressure and heart rate were measured from the tail of rats by Volume Pressure Recording (VPR) sensor technology (10) using Kent scientific instrument supplied by (CODA) which was available in our animal house laboratory. The study protocol was approved by the Ethics Committee of Hawler Medical University, College of Pharmacy with approval number HMUPH-EC-16-08-2021-292.

Experimental design

The rats were divided by a simple random sampling method into five groups, eight rats each, the first group served as a negative control group (saline), the second group (diet-induced hyperlipidemia and Isoprenaline induced myocardial infarction) didn't receive any treatment served as a positive control group, the third group (diet-induced hyperlipidemia and Isoprenaline induced myocardial infarction) received a daily oral administration of Rosuvastatin for 12 weeks, the fourth group (diet-induced hyperlipidemia, DIH) received Bempedoic acid for 4 weeks as a prophylaxis and then myocardial infarction was induced and Bempedoic acid was continued for the remaining 8 weeks, and the fifth group (diet-induced hyperlipidemia and Isoprenaline induced myocardial infarction) received daily oral administration of Bempedoic acid for 12 weeks. Hyperlipidemia was induced by a diet rich in fat given for about 12 weeks (11). Myocardial infarction was induced by administering Isoprenaline subcutaneously at a dose of 85mg/kg with the second dose after 24 hours of the initial dose (12). Bempedoic acid and Rosuvastatin were administered at 30mg/kg/day and 5mg/kg/day respectively (13, 14). The drugs were prepared daily as solutions and administered through an oral route to the rats by using oral gavage needles. At the end of the experiment period, blood samples were withdrawn by cardiac puncture after the rats were anesthetized by injecting a combination of xylazine and ketamine intraperitoneally in a dose of (10mg/kg) and (75mg/kg) respectively (15) for measuring lipid profiles, renal function test, liver function test and random blood sugar. Blood pressure and heart rates were measured and evaluated before and after administration of the drug for each group.

Laboratory investigations and biochemical assays

Rat's lipid profiles were measured using (Cobas Integra 400 plus) special kit while cardiac enzymes were measured by utilizing a special reagent for each of the (CK-mb and Troponin I) using (Cobas-e 411) analyzer.

Experimental Data Processing

Data were analysed statistically using a statistical Package for Social Sciences (SPSS, Version 25). All the data were expressed as Mean ± standard error. Paired t-test was used to compare the data before and after drug administration. One-way analysis of variance (ANOVA) was used for mean comparison and post hoc test (LSD) was also used after (ANOVA) for mean comparison between the two groups. A P-value of ≤ 0.05 was considered statistically significant.

Results

Effects of Bempedoic acid and Rosuvastatin on mean serum levels of lipid profile

The mean serum levels of lipid parameters (Tch, LDL, TG,) of rats in the positive control group were significantly ($P \leq 0.0001$) higher and mean HDL serum levels were lower statistically ($P \leq 0.039$) compared with rats of the negative control group (table 1).

Daily administration of Bempedoic acid as a prophylaxis or treatment and Rosuvastatin for 12 weeks in rats resulted in a significant ($P \leq 0.001$) reduction in the mean of total cholesterol, LDL and triglyceride serum levels respectively and a significant ($P \leq 0.011$, $P \leq 0.001$, ≤ 0.018) increase of mean HDL serum levels respectively compared to control positive group (table 1).

A non-significant ($P > 0.05$) difference in the mean serum levels of Total cholesterol, LDL, TG and HDL were observed after Bempedoic acid administration compared to those of the control negative group (table 1).

With the exception of the mean serum levels of Tch of the Rosuvastatin treatment group that was significantly ($P \leq 0.032$) higher compared to those of the control negative group, the other lipid parameters (LDL, TG and HDL) mean serum levels were significantly ($P \geq 0.957$) ($P \geq 0.688$) ($P \geq 0.735$) not different than those of control negative group rats (table 1).

Rats in the Bempedoic acid prophylactic group showed a statistically significant ($P \leq 0.028$) lower level of Tch

Table 1. Effects of Bempedoic acid and Rosuvastatin on mean Serum levels of lipid profile.

Rat groups	LDL ± SE	Cholesterol ± SE	TG ± SE	HDL ± SE
Negative control	62.29±12.56 acde	66±3.94 ade	61±7.42 acde	22±1.49 acde
Positive control	156.37±10.03 b	169±10.53 b	148.62±6.87 b	16.75±2.44 b
Rosuvastatin	62.95±5.87 cade	87.28±5.60 ce	56.85±8.33 cade	22.85±1.65 cade
Bempedoic acid (prophylaxis)	58.16±6.30 dace	64.5±3.92 dae	65±4.17 dace	23.66±1.40 dace
Bempedoic acid	62±5.62 eacd	82.75±4.38 eacd	44.12±7.20 eacd	25.37±1.22 eacd

Similar letters indicate non-Significant differences and different litters are considered statistically significant at P ≤0.05.

compared with the Rosuvastatin group but in other lipid parameters (LDL, TG and HDL) both Bempedoic acid as therapy or prophylaxis showed a non-significant (P >0.05) difference compared with Rosuvastatin group.

Effects of Bempedoic acid and Rosuvastatin on mean Serum levels of cardiac enzymes

A statistically significant (p≤ 0.0001) higher mean serum levels of troponin I were found in positive control group rats compared with those of negative control, Rosuvastatin and BA groups (table 2).

Rats received Bempedoic acid as a prophylaxis or treatment showed a statistically non-significant (P ≥0.065) (P ≥0.299) difference respectively compared with Rosuvastatin treated rats but both Rosuvastatin and Bempedoic acid as prophylaxis or therapy groups showed a statistically significant (p≤ 0.001) (p≤ 0.015) (p≤ 0.001) higher level of troponin I respectively compared with rats in the negative control group (table 2).

Rats received Bempedoic acid as a prophylaxis showed a statistically significant (p≤ 0.001) reduction in mean serum levels of CK mb compared with rats in the positive control group, Rosuvastatin group and rats received Bempedoic acid as a treatment while showed a statistically non-significant (P ≥0.348) difference compared with rats in the negative control group (table 2).

Rats received Bempedoic acid as a therapy showed a significant (p ≤0.001, P ≤0.017) reduction in mean CK-mb serum levels compared with positive control and Rosuvastatin treated groups respectively but significantly (p≤ 0.001) higher than those of the control negative group and prophylactic BA group (table 2).

Rats treated with Rosuvastatin showed a statistically significant (p≤ 0.001) reduction in CK mb level as compared with a positive control group and a statistically significant (p≤ 0.001) higher level as compared with rats received Bempedoic acid as a prophylaxis and treatment (Table 2). Rosuvastatin received rats also showed a statistically significant (p≤ 0.001) higher level in CK mb levels when they were compared with the negative control group.

Effects of Bempedoic acid and Rosuvastatin on systolic and diastolic blood pressure and heart rate before and after drug administration

A non-significant (P ≥0.098, P ≥0.306 and P ≥0.925) differences in systolic, diastolic blood pressure and heart rate respectively were observed in the positive control group (hyperlipidemia and MI-induced) as shown in (table 3). There was no significant (P ≥0.45, P ≥0.89, P ≥0.073, P ≥0.198) differences in the mean systolic and diastolic blood pressure of rats received BA as therapy or Rosuvastatin treatment respectively compared with the same rats before starting drug therapy (Table 3), While the mean heart rate was reduced significantly (P ≤0.001 and P ≤0.008) respectively as compared to before drugs administration (Table 3).

A significant (P ≤0.002) reduction in systolic and a non-significant (P ≥0.386) change in diastolic blood pressure were observed in BA prophylactic group as shown in (table 3), and the mean heart rate was reduced significantly (p≤0.012) as compared to same rats before drug administration (table 3).

Discussion

In the current study, the administration of Bempedoic acid in a dose of (30mg/kg/day) as a prophylaxis or treatment and Rosuvastatin in a dose of (5mg/kg/day) for 12 weeks showed a significant reduction in lipid profile

Table 2. Effects of Bempedoic acid and Rosuvastatin on mean Serum levels of cardiac enzymes level.

Rat groups	CK mb ± SE	Troponin I ± SE
Negative control	2.1±0.01 ad	0.21±0.032 a
Positive control	145.62±3.38 b	16.43±1.77 b
Rosuvastatin	34.94±3.61 c	7.88±0.93 cde
Bempedoic acid (prophylaxis)	6.05±2.06 da	4.61±0.67 dce
Bempedoic acid	25.25±2.66 e	6.20±1.08 ecd

Similar letters indicate non-Significant differences and different litters are considered statistically significant at P ≤0.05.

Table 3. Effects of Bempedoic acid and Rosuvastatin on Systolic, diastolic blood pressure and heart rate before and after drug administration.

Rat groups	Systolic (before) mmHg ± SEM	Systolic (after) mmHg ± SEM	P value Sig. (2-tailed)
Positive control	151.1±1.82	146.80±1.73	0.098
Rosuvastatin	105.45±1.93	101.06±1.65	0.073
Bempedoic acid (prophylaxis)	89.47±1.39	84.06±0.85	0.002
Bempedoic acid	92.05±2.29	90.45±1.83	0.457
Rat groups	**Diastolic (before) mmHg ± SEM**	**Diastolic (after) mmHg ± SEM**	**P value Sig. (2-tailed)**
Positive control	97.96±1.65	99.12±3.60	0.306
Rosuvastatin	87.14±2.7	80.12±2.49	0.198
Bempedoic acid (prophylaxis)	69.78±3.31	63.33±4.11	0.386
Bempedoic acid	69.92±1.31	69.71±1.40	0.897
Rat groups	**Heart rate (before) beats/min ± SEM**	**Heart rate (after) beats/min ± SEM**	**P value Sig. (2-tailed)**
Positive control	142.12±9.34	143.25±3.22	0.925
Rosuvastatin	107.28±2.31	100.57±1.91	0.008
Bempedoic acid (prophylaxis)	107.16±4.43	96.66±1.92	0.012
Bempedoic acid	107.25±1.76	98.12±1.40	0.001

(Total cholesterol, LDL and Triglyceride) and significant increment in HDL level as compared with a positive control group is obviously attributed to the actions of BA and Rosuvastatin on inhibiting the biosynthesis of cholesterol that results in increased expression of LDL receptors and hypolipidemic effects. The significant beneficial effects of statins and BA on lipid profiles have also been demonstrated by numerous clinical trials and randomized controlled studies (16, 17). Although, Rosuvastatin induced a significant ($P < 0.0001$) reduction in mean Tch serum levels compared to the positive group, however, the mean serum levels of Tch after Rosuvastatin administration were significantly ($P \leq 0.032$) higher than those of control negative group rats, while the mean Tch serum levels following BA administration after induction of MI was non-significantly ($P= 0.077$) different than those of control negative group similar to the BA prophylactic group ($p=0.880$). This could be attributed to the difference in the pathway of inhibition of cholesterol biosynthesis since BA inhibits ACL an enzyme that lies two steps upstream of HMG-CoA reductase that is inhibited by statins (5). This illustrates the greater beneficial effects of BA on total cholesterol levels and coincides with the results of other studies that reported a reduction in LDL-C serum levels was 15% greater by BA than by Statins (18). These results mean that BA could be considered a suitable alternative lipid-lowering agent in patients who require an additional reduction in total cholesterol levels or in a patient with statin intolerance. The disruption of normal cardiac myocyte membrane integrity in myocardial injury results in loss of intracellular constituents into extracellular space (including blood) of a variety of biologically active cytosolic and structural proteins such as troponin and creatine kinase and so both enzymes are considered recommended and reliable biomarker for myocardial injury (19).

The significant ($p\leq 0.001$) difference in the mean serum levels of troponin I that was evident in positive control group rats compared with those of the negative control group indicates that a sufficient number of myocytes have died and lost function due to myocyte necrosis induced by Isoprenaline administration in the present study. The administration of Bempedoic acid as prophylaxis or therapy and Rosuvastatin to rats resulted in a significant ($P \leq 0.0001$) reduction in mean serum levels of cardiac enzymes level compared with those of the positive control group indicating that both drugs had produced cardio-protective effects by significantly alleviating myocardial damage and reserved modulation of the heart that was induced by Isoprenaline in this study. It is noteworthy that rats that received BA as a prophylaxis or as a therapy had significantly ($P \leq 0.001$) ($P \leq 0.017$) lower mean serum levels of Ck-mb levels than those of the Rosuvastatin group respectively which indicates that BA had a more protective effect on reducing the severity of myocardial damage induced by Isoprenaline than did Rosuvastatin. The non-significant ($P\geq 0.065$) ($P\geq 0.29$) differences respectively in the mean serum levels of troponin I following BA prophylaxis or treatment than those of the Rosuvastatin group indicate that BA was not superior to Rosuvastatin in reducing the severity of myocardial injury since troponin I which is a highly specific marker of the heart stays high longer than Ck-mb following myocardial injury.

Administration of BA as prophylaxis to one group of rats is noted to decrease both Troponin I and CK-mb by a greater percentage compared to both the BA treatment group and the Rosuvastatin group which indicates that using BA as a prophylaxis could decrease the incidence of atherosclerotic cardiovascular diseases in those that are at high risk of getting these illnesses.

On the other hand, in the current study, administration of BA as therapy and Rosuvastatin didn't produce significant change ($P \geq 0.45$, $P \geq 0.89$, $P \geq 0.073$, $P \geq 0.198$ mmHg) in systolic and diastolic blood pressure respectively compared with the same rats before drug administration while BA prophylactic group showed a significant ($P \leq 0.002$) reduction in systolic and non-significant ($P \geq 0.386$) change in diastolic blood pressure. In a previous post-hoc analysis of patients with slightly elevated blood pressure,

it was observed that the administration of BA reduces blood pressure (20). While in a newly completed double-blind placebo-controlled trial, the BA effect on blood pressure was completely neutral (21). Although statins have been shown to reduce blood pressure by promoting the release of nitric oxide (NO) and are associated with better ambulatory blood pressure control according to several studies (22, 23), but in our study, Rosuvastatin didn't show any significant reduction in blood pressure compared to baseline blood pressure level before starting drug administration and this result could be contributed to the short of study period (12 weeks) and a small number of rats.

Conclusions

The findings from this study suggested that Bempedoic acid as monotherapy either as a therapy or as a prophylaxis was effective in reducing lipid parameters, LDL, Tch, and TG and cardiac enzymes creatine kinase-MB (CK-MB) and serum level of cardiac troponin-I (cTn-I) compared with a positive control group and was not superior to Rosuvastatin in these parameters but taking BA as prophylaxis could prevent the morbidity with cardiovascular events as it was effective in reducing the above parameters by greater percentages than BA and Rosuvastatin therapy.. Both drugs showed similar profiles in blood pressure and heart rate measurements.

Acknowledgements

None.

Conflict of interest

The authors declare no conflict of interest.

Availability of data and material

All data generated during this study are included in this published article.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Hawler Medical University, College of Pharmacy.

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