Bulletin of Faculty of Pharmacy, Cairo University (2016) xxx, xxx–xxx

Cairo University

Bulletin of Faculty of Pharmacy, Cairo University

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ORIGINAL ARTICLE

# Effect of Amlodipine, Cilnidipine and Diltiazem on lipid profiles of hypertensive rats fed with high fat diet: A comparative study

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Received 15 July 2015; revised 15 March 2016; accepted 11 April 2016

**KEYWORDS**

Calcium channel blockers;
Hypertensive rats;
High fat diet;
Hypolipidemic effect

**Abstract** *Objective:* The present study was aimed to compare the effect of calcium channel blocker (Amlodipine, Cilnidipine and Diltiazem) on lipid profiles of hypertensive rats fed with high fat diet for four weeks.
*Methods:* Hypertensive rats were randomly allocated into four groups and except hypertensive rats remaining all groups received high fat diet for 4 weeks. At the end of protocol blood pressure was measured by tail cuff method and blood is withdrawn from the retro-orbital puncture, separated serum is used for the assessment of various biochemical parameters. Finally liver and aorta isolated for histological changes.
*Results:* Calcium channel blocker significantly reduces the lipid levels raised in hypertensive rats fed with high fat diet and also restore the pathological changes of aorta and liver tissues.
*Conclusion:* These results indicate that they have a lipid lowering effect due to effect on different stages of metabolism of lipids.
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## 1. Introduction

Calcium channel blockers (CCBs) are commonly used for various cardiovascular diseases like hypertension and ischaemic heart disease.[1] They are chemically classified into phenylalkylamines, dihydropyridines, and benzothiazepines.[2] Even though hypertension participated in the progression of atherosclerosis, the exact mechanism hasn't been ruled out yet.[3] Hence the effect of calcium antagonists on serum lipids and lipoproteins is of increasing interest. Current therapeutic interventions for the prevention of cardiovascular disease are directed at established risk factors such as hypertension, dyslipidemia (elevated low density lipoprotein [LDL]-cholesterol, triglycerides as well as decreased high-density lipoprotein [HDL]-cholesterol), and hyperglycaemia.[4]

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Peer review under responsibility of Faculty of Pharmacy, Cairo University.

http://dx.doi.org/10.1016/j.bfopcu.2016.04.001
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Please cite this article in press as: Dangi NB et al. Effect of Amlodipine, Cilnidipine and Diltiazem on lipid profiles of hypertensive rats fed with high fat diet: A comparative study, *Bulletin Facult Pharmacy Cairo Univ* (2016), http://dx.doi.org/10.1016/j.bfopcu.2016.04.001

Over the past 30 years, considerable experimental and clinical evidence has accumulated to support the suggestion that calcium channel blockers (CCBs) have significant anti-atherosclerotic effects that are independent of their hypotensive effects.[5]

The accumulation of information in the last decade has suggested several cellular mechanisms for CCBs which may influence atheroma;[6] (a) Inhibition of vascular smooth muscle cell proliferation and migration (b) inhibition of calcium influx and deposition in the arterial wall (c) inhibition of synthesis and deposition of extracellular matrix (d) enhanced removal and degradation of cholesterol rich lipoproteins (e) protection of LDL from oxidation (f) inhibition of platelet activation and (g) preservation of endothelial function and hemodynamic effect.

The present study investigates the comparative effect of Amlodipine, Diltiazem and Cilnidipine on the lipid profile of rat fed with high cholesterol diet.[7] Amlodipine is a widely used drug for hypertension and Cilnidipine is a new calcium channel blocker approved for treatment of hypertension, whereas Diltiazem is used for various other cardiovascular diseases. Studies also include a histopathological investigation to assess cellular damage and improvement after the drug treatment in different groups.

## 2. Materials and methods

### 2.1. Chemicals

Cholesterol, sodium cholate, cocoa butter and coconut oil were purchased from national chemicals, Baroda. All other reagents and chemicals obtained were of analytical grade. Amlodipine was dissolved in 0.5% DMSO solution and diluted to required volume with water. Diltiazem was freely dissolved in distilled water; Cilnidipine was prepared in a 0.5% DMSO solution.

### 2.2. Animals

All experiments and protocols described in the present study were approved by the Institutional Animal Ethics Committee (IAEC) of Pharmacy Department, The M.S. University of Baroda and with permission from the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India. Healthy Wistar rats of either sex weighing between 200 and 300 g were housed in polypropylene cages and maintained under standardized conditions (12-h light/dark cycle, 24 ± 2 °C, 35 to 60% humidity) and provided free access to palleted CHAKKAN diet (Nav Maharashtra Oil Mills Pvt. Ltd., Pune) and purified drinking water *ad libitum*. All animals were acclimatized for one week before the experiment started.

### 2.3. Induction of hypertension: DOCA-salt-induced hypertension

Hypertension was induced experimentally in Male Wistar rats (200–250 g) by unilateral nephrectomy.[8] Rats were anaesthetized with ketamine (100 mg/kg body weight), and a lateral incision was made in the area overlying the kidney. The renal blood vessel was ligated with fine sterile silk thread and the kidney was removed. The incision was sutured and closed with Michel clips. All operated rats received an injection of ampicillin (10 mg/kg, i.p.) daily for 5 days. Neosporin powder (polymyxin B sulfate BP, zinc bacitracin BP, neomycin sulfate IP) was applied locally to prevent infection. One week later, Deoxycorticosterone acetate (DOCA) (20 mg/kg, twice a week; s.c., for 4 weeks) dispersed in olive oil was injected into uninephrectomized rats. A solution of 1% saline + 0.2% KCl *ad libitum* was given instead of drinking water. In sham-operated control animals, a similar procedure was performed except the treatment with DOCA.

### 2.4. Composition of high cholesterol diet and its preparation

Cholesterol (0.5%), Sodium cholate (0.1%), Cocoa butter (10%), Coconut oil (10%) and Pellet powder (79.4%)

### 2.5. Preparation of diet

79.4 gm. of pellet powder was mixed with 100 mg of sodium cholate separately. Simultaneously 500 mg of cholesterol and 10 gm. of cocoa butter were dissolved in 10 ml of warm coconut oil. This oil solution of cholesterol was added slowly into the powdered mixer to obtain a soft homogenous cake. This cake was molded into pellets.

### 2.6. Experimental design

Rats were randomly divided into the following groups. Each group consists of six animals.

*Group 1:* Sham control: They were fed with standard laboratory diet and water *ad libitum* for four weeks.

*Group 2:* DOCA induced hypertensive rats: They were fed with high cholesterol diet +0.5% DMSO[9] for four weeks.

*Group 3:* DOCA induced hypertensive rats + Amlodipine: They were administered Amlodipine (5 mg/kg, p.o) for four weeks along with high cholesterol diet.

*Group 4:* DOCA induced hypertensive rats + Diltiazem: They were administered Diltiazem (30 mg/kg, p.o) for four weeks along with high cholesterol diet.

*Group 5:* DOCA + Cilnidipine: They were administered Cilnidipine (10 mg/kg, p.o) for four weeks along with high cholesterol diet.

### 2.7. Preparation of serum sample

At the end of 4th week, animals were fasted overnight and hemodynamic study was carried out, then serum and tissue were subjected to different biochemical analysis & histoarchitecture study.

The blood samples were withdrawn from the retro-orbital plexus under light ether anesthesia and allowed to clot for 10 min at room temperature. It was centrifuged at 2500 RPM for 20 min. The serum obtained was kept at 4 °C until used.

After blood collection, all the animals were sacrificed by ether anesthesia followed by spinal dislocation. Liver and aorta were removed in a chilled condition and immediately placed in 10% buffered formalin, embedded in paraffin, cut

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