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Atorvastatin in nano-particulate formulation abates muscle and liver affliction when coalesced with coenzyme Q10 and/or vitamin E in hyperlipidemic rats

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ABSTRACT

Aims: Statins are the most widely used to lower elevated low-density lipoprotein levels and preventing cardiovascular diseases in humans. However, about 20% of patients treated with this medication suffer from statin-related myalgia. To this end, this study investigated the potential effect of nano-particulate formulation in alleviating the muscles and liver damage either alone or when co-administered with nano coenzyme Q10 and nano vitamin E.

Materials and methods: Male Wistar rats were fed normal diet or high-fat diet for 12 weeks, following which rats were treated with either (i) atorvastatin (5 or 20 mg/kg/day, p.o.) or (ii) atorvastatin with CoQ10 (10 mg/kg/day, p.o.) (iii) and/or vitamin E (30 mg/kg/day, p.o.) in free particle or nanoparticle forms for another 4 weeks. In all rats, serum total cholesterol (CH), triglycerides (TGs), low (LDL) and high (HDL) density lipoproteins, alanine (ALT) and aspartate (AST) transaminases, alkaline phosphatase (ALP), creatine kinase (CK), albumin (ALB), as well as hepatic malondialdehyde (MDA) and antioxidants "reduced glutathione (GSH) and superoxide dismutase (SOD)" were measured. Additionally quadriceps muscles and liver tissues were used for histopathological examination.

Key findings: The antihyperlipidemic effect of statins was not altered when formulated as nanoparticles; albeit the former showed a prominent reduction in the liver and muscle enzymes and histopathological alterations together with a marked decline in the oxidative stress as compared to the free particulate form. These results were augmented when atorvastatin was combined with CoQ10 and/or Vit.E.

Significance: Nanoparticulate formulation alleviated the statins induced liver and muscle damage especially when combined with CoQ10 and/or Vit.E.

1. Introduction

Hyperlipidemia is a condition in which there is an increase in levels of lipids in the blood, including cholesterol, triglycerides and lipoproteins [1]. According to the World Health Organization, it has recently reported that hyperlipidemia is significantly associated with almost half of global cases of ischemic heart diseases [2]. Consequent to hyperlipidemia, the hardened arteries will block blood flow to the brain and limbs as well as the heart, causing, stroke [3], peripheral vascular disease [4] and coronary artery disease (CAD) [5], respectively.

At the heart of our understanding, through inhibition of the key enzyme, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) in cholesterol biosynthesis, statins are used as an effective treatment for hypercholesterolemia [6]. Although statin therapy targets reduction in LDL-CH, some studies have shown an increase in high-density lipoproteins [7]. Despite the clinical success associated with statins use, a variety of complications are associated with its therapeutic effect [8–11]. A leading problem is the statin-induced myopathies associated with long-term therapy, which extends from mild myopathy to fatal rhabdomyolysis. Cerivastatin (Baycol®) was placed off the market in 2001 following 100 rhabdomyolysis-related deaths associated with the drug use [12]. Statin associated myopathy (SAM) affects > 20% of patients leading to lack of adherence to statin therapy [13]. Another impediment with statin therapy is hepatotoxicity, characterized by an elevation of liver enzymes [14]. Patterns of liver abnormalities seen with statins include hepatitis, cholestatic or mixed hepatitis and drug-induced liver injury (DILI).

Thorough investigation with statins showed that it decreases the

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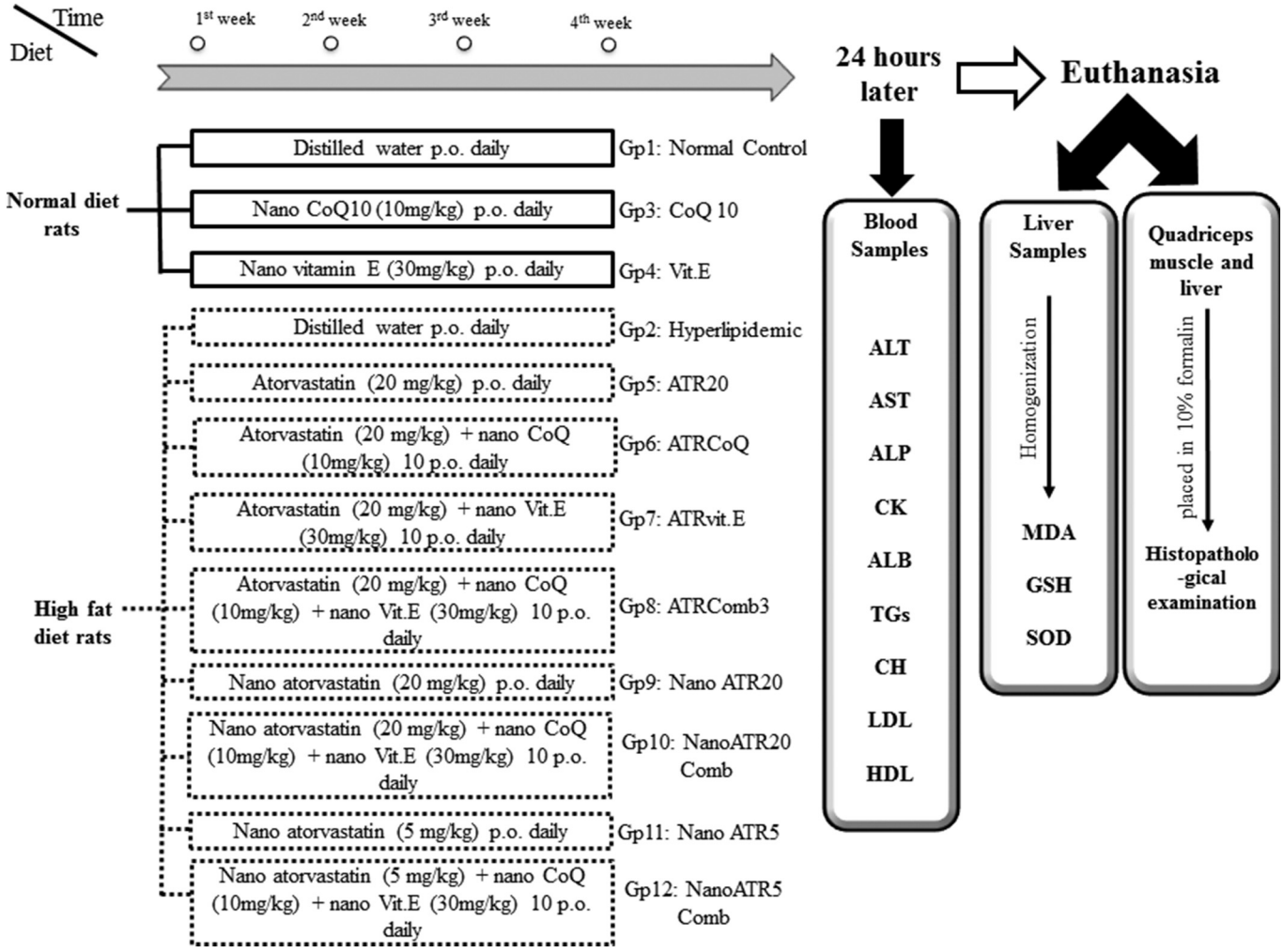

Fig. 1. Experimental design portraying the allocation of rats in different control and treatment groups. Rats were fed normal or high fat diet and exposed to the assigned treatment for 4 weeks. 24 hour post-exposure blood samples were taken and used for biochemical estimations in blood then the rats were euthanized and liver and quadriceps muscle were isolated for biochemical estimations and histopathological examination.

biosynthesis of mevalonate and ubiquinone which are electron carriers linking the electron transport chain in mammalian mitochondria. Existing research recognizes the role of coenzyme Q10 (CoQ10) in increasing levels of these mediators causing inhibition of LDL peroxidation [15,16]. A growing body of literature affirms that statins decreased blood levels of fat soluble components such as vitamin E [17]. Studies confirmed that vitamin E (Vit.E) plays a vital role in maintaining the proper skeletal muscle homeostasis [18].

Currently, nanoscience and nanotechnology have gained global attention to help improve the bioavailability of a given medication [19]. At the beginning of the 1990s, solid lipid nanoparticles (SLNs) were developed as alternative carrier system to the conventional carriers [20]. Their advantages over other polymeric nanoparticles in drug delivery administration include good tolerability [21], physical stability, and protection of labile drugs from degradation [19]. Additionally, SLNs can be used to obtain sustained release of lipophilic drugs like atorvastatin decreasing its adverse effects [22].

In light of the previous reported events, it is becoming problematic to ignore the existence of toxicities associated with atorvastatin therapy and heightened the need to reduce the impact of these disorders without affecting the therapeutic power of statin therapy. To this end, the first section of this study will explore, for the first time, the effects of CoQ10 and Vit.E in nanoparticulate form when used in combination with atorvastatin. Hitherto, no attention has been paid to administer CoQ10 and Vit.E in their nano formulation in the aim of protection against atorvastatin side effects, and hence this work aimed to decipher this attribute. The key question that this piece of work addressed is whether SLNs could contribute in improving the pharmacodynamics of atorvastatin or not unlike other studies which focused only on the improvement in bioavailability and pharmacokinetics of these drugs.

2. Material and methods

2.1. Animals

Adult male Wistar rats weighing; 120–150 g were obtained from the National Scientific Research Centre (Giza, Egypt). Animals were housed for at least 1 week in the laboratory room prior to testing. They were kept under controlled environmental conditions; room temperature (23 ± 4 °C), constant humidity (60 ± 10%), with alternating 12 h light and dark cycles. Food (standard pellet diet) and water were allowed ad libitum. Experiments were conducted during light phase of the cycle. All experiments were performed according to the protocol approved by the Ethics Committee of Faculty of Pharmacy Cairo University (Permit Number: 1349) in strict accordance with the international policies (Guide for Care and Use of Laboratory Animals published by the US National Institute of Health; NIH Publication No. 85-23, revised 1996). Unnecessary disturbance of animals was avoided. Animals were treated gently; squeezing, pressure and tough maneuver were avoided.