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The Effect of Magnesium Hydroxide Nanoparticles on Lipid-Profile of Ibuprofen-Induced Stomach-Ulcer in Adult Male Albino Rats

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Abstract

Back ground-Many therapeutic agents have been developed for the treatment of ulcer, but the quest for more effective and affordable drugs has continued. This study was aimed at determining the effect of magnesium hydroxide nanoparticles on lipid-profile of ibuprofen-induced stomach-ulcer in adult male albino rats. **Methodology**-Thirty adult male rats weighing between 130 and 160 grams were randomly divided into five groups (G1-G5) of six animals. G1 (normal control) received 1 ml of distilled water per day, G2-G5 were treated with 400 mg/kg body of ibuprofen to induce stomach-ulcer, G3-G4 received 100 and 200 mg $Mg(OH)_2$ nanoparticles respectively, while G5 received 20 mg of omeprazole as a standard drug. The animals were administered with the drug for two weeks, with free access to food and water. **Results**- This showed that at 400 mg/kg, ibuprofen received by the animals caused a significant decrease in their total cholesterol and high-density lipoprotein cholesterol levels ($p<0.05$), and increased significantly the low-density lipoprotein cholesterol, but did not significantly increase the plasma triglyceride level as against the normal control($p<0.05$). A dose-dependent and significant increase in the plasma total cholesterol and HDL levels ($p<0.05$) ,was observed in rats administered between 100 and 200 mg/kg nanoparticles (69.23 ± 9.04 and 133.93 ± 5.52) and (60.49 ± 5.22 and 69.98 ± 12.20), as against the group treated at 400 mg/kg (23.66 ± 11.86 and 54.50 ± 20.20) respectively. Conversely, the nanoparticles at the aforementioned concentrations reduced plasma low-density lipoprotein cholesterol and triglycerides level significantly ($p<0.05$). **Conclusion**- Magnesium hydroxide nanoparticles could be useful in treating hyperlipidemia- related diseases, one of the major risk factors for atherosclerosis.

Key words: Ibuprofen-induced, Lipid-profile,Magnesium hydroxide, Nanoparticles, Stomach-ulcer

1.Introduction

Research has proven that drugs that are transformed into nano ranges offer some unique features such as prolonged circulation, improved drug localization and enhanced drug efficacy (Bhatia, 2016). In delivering therapeutic compounds to the desirable sites, poor bio-distribution, limited effectiveness, undesirable side effects, and lack of selectivity are bound to occur (Bhatia, 2016). To overcome these, drugs had to be transformed into nano ranges (nanoparticles) so as to acquire a great potential aimed at concentrating them and as well as targeting the desired diseased tissue(s) which aids in reducing toxicity, enhancing release, improving solubility and bioavailability (Goldberg *et al*., 2011).

The nanoparticle-based drugs had been used to treat various ailments such as ulcer. Pathologically, ‘‘ulcer refers to as the breach of the continuity of skin, epithelium or mucous membrane caused by sloughing out of inflamed necrotic tissues’’ and this tends to completely alters the metabolic organogram of the affected tissues (Milind & Wen, 2015). Most ulcers (Peptic, gastric, duodenal, oesophageal and refractory etc.) are caused by a bacterium, the *Helicobacter pylori*, excess acids and gastric juices secreted by the stomach, and they are characterized by abdominal pain, heartburn (acid reflux), discomfort after meals, anemia, weight loss, poor appetite, constipation, vomiting etc. (Yu *at al*., 2017).

Various therapeutic agents have been developed for the treatment of ulcer but the quest for more effective and affordable drugs had continued. Magnesium hydroxide $Mg(OH)_2$ as an antacid works by simple neutralization, where the hydroxide ions from the $Mg(OH)_2$ combine with acidic H^+ ions produced in the form of hydrochloric acid by parietal cells in the stomach to produce water (Margarete *et al.*, 2005). It has been established that there is a positive correlation between serum Mg $(OH)_2$ and lipid metabolism in atherosclerotic cardiovascular disease in general population and dialysis patients (Baradaran & Nasri, 2004; Sidhu & Naugler, 2012). The intervention of Mg $(OH)_2$ nanoparticles in the mediation of lipid dysfunction in gastric ulcerated adult male albino rats was investigated.

2 Materials and Methods

2.1 Experimental Animals

Thirty male adult albino rats of 130-180 g were procured from the Animal House of College of Medicine, Ekiti State University, Ado-Ekiti. The experimental animals were randomly divided into five groups of six animals each, and allowed to acclimatize to experimental condition for two weeks. They were housed in clean cages and maintained under standard laboratory conditions (temperature 25±2ºC with dark/light and were fed ad libitum on rat pellets by (Top Feeds, Nigeria) and water. The procedures adopted in this study were in accordance with Guidelines for Care and Use of Laboratory Animals in Biomedical Research of the National Institutes of Health of the United States (NIH, 1985).
Note: All the necessary chemicals and reagents used in this work were of analytical grade and were purchased from Sigma-Alrich (St-Louis, MO, USA).

2.2 Experimental Design

G 1: normal albino rats (control) received 1 ml of distilled water per day for seven days. G 2: received ibuprofen, 400 mg/kg body weight before they were fasted and sacrificed. G 3: received 100 mg magnesium hydroxide nanoparticles as prevention. G 4: received 200 mg magnesium hydroxide nanoparticles as prevention. G 5: received 20 mg omeprazole, as a standard drug for stomach ulcer treatment. Omeprazole solution was prepared by dissolving about 28.8 mg of the drug in 10.8 ml of distilled water and administered daily at approximately 3.85 mg/kg for seven days. On the seventh day, stomach ulcer was induced using ibuprofen. All suspensions were administered orally to the animals and they were starved of their feed and water for the period of seven hours. Thereafter, they were mildly anaesthetized with chloroform and sacrificed. The blood plasma was collected from the heart into ETDA bottle.

2.3 Determination of Biochemical Parameters

2.3.1 Total Cholesterol:

LDL-Cholesterol and **Triglyceride** were determined according to the method described in Lipid Research Clinical Program Manual of Laboratory Operations, (NIH,1984).

2.3.2 HDL-Cholesterol

This experiment was carried out using the method described by Lopes-Virella, *et al*., (1977).

2.4 Statistical analysis

The experimental data were analyzed statistically using ANOVA and the results were presented as Mean ± Standard deviation at ($p<0.05$). The SPSS v 21 was used for the analysis.

3 Results

From the table 1 below, there was significant ($P<0.05$) decrease in the weight gain of the test groups, except G5, compare to the normal control (G1).

Table 1: Differences in weight of the experimental animals

Weight of the animals	G1	G2	G3	G4	G5
Final	175 ± 1.00^{a}	182 ± 1.50^{b}	192 ± 2.00^{c}	199 ± 1.50^{d}	225 ± 2.50^{e}
Initial	130 ± 3.00^{a}	145 ± 1.00^{b}	153 ± 2.60^{c}	178 ± 1.00^{d}	180 ± 1.00^{d}
Weight gain	45 ± 1.00^{d}	36 ± 0.30^{b}	39 ± 0.90^{b}	21 ± 1.00^{a}	46 ± 1.50^{d}

Data are Mean ± SD, n=6. Values with different superscripts indicate significant difference at $p<0.05$.

The results (table 2) showed that the G2 treated with 400 mg of ibuprofen decreased significantly ($p<0.05$) the total cholesterol and high Density Lipoprotein Cholesterol levels, and increased significantly the low density lipoprotein cholesterol but did not significantly ($p> 0.05$) increase the plasma triglyceride level as against the normal control. However, a dose-dependent and significant increase ($p<0.05$) in the plasma total cholesterol and HDL levels were observed in rats administered between 100 and 200 $Mg(OH)_2$ mg/kg nanoparticles as against the group treated with 400 mg of ibuprofen, respectively.

Table 2: Effect of magnesium hydroxide on plasma lipid profile of ibuprofen-induced gastric ulcerated rats

S/N	TCHOL	LDL	HDL	TAG
G1 (Normal control)	160.22 ± 19.28^{a}	55.14 ± 6.04^{a}	90 ± 8.10^{a}	178.05 ± 22.34^{a}
G2 (400 mg Ibuprofen)	23.66 ± 11.86^{d}	66.37 ± 16.10^{ab}	54.50 ± 20.20^{d}	178.84 ± 24.24^{a}
G 3 (100 mg)	169.23 ± 9.04^{a}	49.47 ± 9.44^{b}	60.49 ± 5.22^{d}	123.31 ± 13.34^{b}
G 4 (200 mg)	133.93 ± 5.52^{b}	55.20 ± 13.10^{a}	69.98 ± 12.20^{cd}	92.10 ± 7.94^{c}
G 5 (20 mg Omeprazole)	31.97 ± 7.15^{d}	68.52 ± 13.32^{ab}	87.33 ± 14.89^{bc}	123.68 ± 8.66^{b}

Data are Mean ± SD, n=6. Values with different superscripts indicate significant difference at $p<0.05$.

4. Discussion

The use of Mg(OH)2 nanoparticles for therapeutic interventions in dyslipidemia amongst ulcer patients is receiving attention. From the table 1, there was a significant (p<0.05) decrease in the weight gain of the test groups, except G5, compare to the normal control (G1). The observed decrease in the weight gain of the test groups could be as a result of reduced feed intake, poor nutrient absorption and utilization. Alterations in the concentration of major lipids like total cholesterol, low density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides could predispose the heart to atherosclerosis and its associated coronary heart diseases (Yakubu *et al*., 2008).

As observed on this work, the group (G5) treated with 20 mg omeprazole, did not increase the plasma total cholesterol level significantly (p<0.05) compared with the untreated group (G2). However, significant increase was recorded in groups (G3 and G4) treated with 100 mg and 200 mg magnesium hydroxide nanoparticles, respectively, with respect to G2 and G5. This could be possibly attributed to the ability of the magnesium hydroxide nanoparticles to increase cholesterol esterase and stimulation of HMG-COA reductase activity in those groups. Also, nano particles have been identified to possess high biologic activity as a result of their ability to transfer easily through cell membrane, which might be one of the reasons for their numerous applications especially in treatment of different diseases. This finding corroborates that of Noushin and Shaghayegh, (2014) and Hoet *et al.*, (2004) where approximately a similar result was recorded.

Induction of stomach ulcer with ibuprofen triggered significant increase (P>0.05) of low density lipoprotein cholesterol (LDL). However, administration of the nanoparticles reversed the increased LDL occasioned by the induced stomach ulcer significantly ((P<0.05) when compared with the normal, untreated and the omeprazole treated group. However, an interesting result was observed in the G4 treated with 200 mg of magnesium hydroxide nanoparticles; where approximately and statistically similar result was obtained when compared with the normal rats (G1). This suggests the usefulness and the potent of magnesium hydroxide nanoparticles in treatment of ailments. Decreased LDL concentration as recorded in this work agrees with that of Noushin and Shaghayegh, (2014), where they reported that magnesium oxide nanoparticles decreased LDL concentration.

The effect of magnesium hydroxide nanoparticles on plasma high density lipoprotein (HDL) showed that administration of 200 mg magnesium hydroxide nanoparticles increased the high density lipoprotein cholesterol of the treated experimental animals significantly (p>0.05) ***Int.*** compared to the untreated group. However, the observed value is significantly lower than the data obtained from the group treated with 20 mg omeprazole, the standard drug for the treatment of stomach ulcer. This is in consonance with the finding of Noushin and Shaghayegh (2014). They reported that magnesium oxide has ameliorative effect in lipid profile by increasing HDL and decreases LDL concentration. This could be one of the reasons magnesium serves as a cofactor of numerous metabolic enzymes (e.g. glycolytic pathway enzymes) and plays an important role in lipid metabolism (Elekofehinti *et al*., 2012). HDL has recently been recognized to have several other important cardio-protective properties such as the ability to protect LDL from oxidative modification. HDL plays a protective role in artherogenesis by preventing the generation on an oxidative modified LDL and the mechanism action of HDL may involve exchange of lipid peroxidation products between the lipoproteins (Moridian *et al.*, 2015).

Triglycerides are neutral fats found in the tissues. Triglycerides containing lipoproteins may also contribute to the disorders related to coronary heart disease. Persons with high triglycerides often have other conditions, such as diabetes and obesity, which also increase the chances of developing heart disease (NCEP, 2002; Taylor *et al*., 2011; Mahley, 2016). The reduction in the plasma triglyceride level in the test groups, compared with the G5 (Omeprazole) and the normal, suggests that the nanoparticles have the tendency andpropensity of reducing plasma triglyceride level in the body. However, an interesting result was obtained in the untreated group; where the plasma triglyceride level recorded was not statistically indifferent to that of normal (178.05 ± 22.34^{a}) and untreated (178.84 ± 24.24^{a}) groups respectively.

This could be attributed to the fact that the ibuprofen did not interfere with the lipid content of the experimental animals in G2. The observed hypotriglyceridemic effect of the nanoparticles in G3 and G4 might be due to a decrease in fatty acid synthesis, enhanced LDL receptors, activation of LCAT and lipases and also inhibition of acetyl-coA carboxylase (Lemhadri *et al*., 2006; Mahley, 2016).

Conclusion

Since the magnesium hydroxide nanoparticles reduced the increased triglyceride and low density lipoprotein, commonly known as bad cholesterol, caused by induction of stomach ulcer by ibuprofen, and at the same time increased the concentration of high density lipoprotein good cholesterol) to a significant level ($P > 0.05$) approximately similar to the level found in the normal experimental animals. Therefore, the magnesium hydroxide nanoparticles could be useful in treatment of hyperlipidemia- related diseases, one of the major risk factors for arthrosclerosis.

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Ethical approval

The present research work was permitted by the Afe Babalola University Animal Ethical Committee.

Conflict of interest

We declare that there was no conflict of interest.