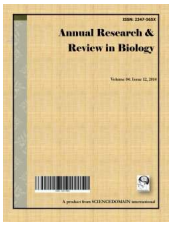

Annual Research & Review in Biology

21(6): 1-11, 2017; Article no.ARRB.38155
ISSN: 2347-565X, NLM ID: 101632869

Effect of Acute Doses of Magnesium Hydroxide Nanoparticles on Some Biochemical Parameters of Wistar Rats

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Authors' contributions

This work was carried out in collaboration between all authors. Authors BTA and OIO designed the study, performed the experiments, statistical analysis and wrote the draft of the manuscript. Authors ORM and YRA managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/ARRB/2017/38155
Editor(s):
(1) Saleha Sadeeqa, Incharge Institute of Pharmacy, Lahore College for Women University, Pakistan.
(2) George Perry, Dean and Professor of Biology, University of Texas at San Antonio, USA.
Reviewers:
(1) Rui Yukui, China Agricultural University, China.
(2) Jiangong Liang, Hua Zhong Agriculture University, China.
(3) André Chwalibog, University of Copenhagen, Denmark.
Complete Peer review History: http://www.sciencedomain.org/review-history/22536

Original Research Article

Received 14th November 2017
Accepted 28th December 2017
Published 30th December 2017

ABSTRACT

Aim: This study was designed to assess the toxic effect of magnesium hydroxide nanoparticles on some biochemical parameters of Wistar rats.
Place and Duration of Study: Department of Biochemistry, Ekiti State University, Ado Ekiti, Ekiti State, Nigeria. Between June and November, 2016.
Methodology: Thirty six rats were randomly distributed into six experimental groups of six animals each. Group 1 served as the control and received distilled water. Groups 2 to 6 were orally exposed to a single dose varying concentrations of magnesium hydroxide nanoparticles at 500, 1000, 2000, 4000 and 5000 mg/kg body weight. The animals were observed daily for signs of toxicity and mortality for 14 days. Thereafter, they were sacrificed and alterations in the haematological parameters, serum lipid profile and some functional indices of the liver and kidney were then evaluated.
Results: The administration of the nanoparticle did not result in mortality of the rats at the tested doses. Also there were no significant ($P<0.05$) alterations in the computed liver- and kidney-body

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weight ratios, serum lipid profile, white blood cells (WBC), lymphocytes, monocytes, eosinophils, urea, sodium, chloride, potassium and glucose levels. The concentrations of mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH) and neutrophils decreased significantly. In contrast, the levels of the red blood cell count (RBC), haemoglobin (Hb), packed cell volume, also, the activities of alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) increased significantly ($P<0.05$). Also the administration of the nanoparticle induced a significant increase in the concentration of malonaldehyde (MDA) formed in the liver and kidney at 1000, 2000, 4000 and 5000 mg/kg.

Conclusion: Although, no mortality was observed, this study suggests that magnesium hydroxide nanoparticles may have mild hepatotoxic effects at the doses investigated.

Keywords: Magnesium hydroxide; nanoparticles; doses; rats.

1. INTRODUCTION

Nanotechnology is a rapidly growing field of research that has attracted the interest of many researchers in various disciplines [1]. Nanoparticles (NPs) are substances with unique physical and chemical properties usually found in environment. Their size ranges between 1 – 100 nm. Due to their size, NPs have large surface area which gives them an edge over other compounds in various applications [2]. They are extensively used in drug delivery systems, production of cosmetics and synthesis of biosensors [3]. Living organisms are constantly exposed to NPs in the environment. There are several types of NPs most of which are metal based. The widespread applications of NPs have raised concerns about the safety of these particles on human health and the environment. Nanoparticles have been reported to induce genotoxicity, inflammatory responses and cellular injury [4,5].

Magnesium hydroxide also known as “the milk of magnesia” is an inorganic compound with the chemical formula $Mg(OH)_2$. Its occurrence in nature is in form of mineral brucite [6]. It is a solid with whitish appearance and low solubility in water. Magnesium hydroxide has a wide range of industrial and medical applications. It is utilized to provide cost-effective solutions to environmental problems [7]. This had been achieved by using this compound for heavy metal precipitation, acid neutralization of industrial wastewater and treatment of flue-gases. It is also used as fertilizer additive and flame retardant in paper industry. In the medical field, magnesium hydroxide is a common antacid excipient. It combines with acidic H^+ ions produced in the form of hydrochloric acid by parietal cells in the stomach to produce water. It has also been shown to have laxative properties [8]. Several methods have been employed for the synthesis of magnesium hydroxide nanoparticle [9,10,11,12]. Research has shown that when magnesium hydroxide is crystallized in the nanoscale size, it enhances its adsorption to its composite [11]. As a result of this discovery, magnesium hydroxide nanoparticle has become a useful tool in environmental remediation processes. It is a precursor for the synthesis of magnesium oxide nanoparticle [8].

Despite the wide usage of magnesium hydroxide nanoparticle, documentations on its safety in living organisms are scanty in scientific literatures. Therefore, this study was designed to unravel the adverse effect of acute doses of this nanoparticle in Wistar rats with a view to ascertain its safety on biological systems and suitability in environmental remediation processes.

2. MATERIALS AND METHODS

2.1 Reagents and Assay Kits

Magnesium hydroxide nanopowder ($Mg(OH)_2$, 99% purity, 10 nm size) was purchased from US Research Nanomaterials, Inc. 3302 Twig Leaf Lane Houston, TX 77084, USA. Thiobarbituric acid (TBA), Hydrochloric acid (HCl), Trichloroacetic acid (TCA), Tris, Potassium chloride (KCl) were obtained from Sigma Chemical Co. (St. Louis, MO, USA). The assay kits for total cholesterol, triacylglycerol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), alkaline phosphatase (ALP), alanine and aspartate aminotransferases (ALT and AST, respectively) were obtained from Randox Laboratories United Kingdom. All other reagents used were of analytical grade.

2.2 Experimental Design

Magnesium hydroxide nanoparticles was studied for acute oral toxicity as per Organization for

Economic Co-operation and Development (OECD) guidelines number 423 [13]. A total of 36 (thirty six) healthy Wistar albino rats (*Rattus norvegicus*) weighing 160–210 g were procured from the Central Animal House, College of Medicine, Ekiti State University, Ado Ekiti, Nigeria for the study. The rats were kept in standard wooden cages placed in a well ventilated animal house (photoperiod of about 12 h light: 12-h dark) throughout the experimental period. They were acclimatized for a period of 2 weeks prior to the administration of the nanoparticles. The rats were fed with normal rat pellets and water *ad libitum*. The care of the animals was done in accordance with the criteria outlined in the 'Guide for the Care and Use of Laboratory Animals' prepared by the National Academy of Science and published by the National Institute of Health. The rats were randomly divided into 6 groups with 6 animals per group. Group 1 served as the control and was administered 1 ml of distilled water. Groups 2 – 6 were administered single oral dose of 500, 1000, 2000, 4000 and 5000 mg/kg, p.o. of the nanoparticle. The animals were monitored individually during the first 30 min and thereafter 24 hourly for a period of 14 days. Signs of toxicity, mortality, feed and water intake for each group was observed everyday for 14 days. At the end of the study, all animals were sacrificed by cervical dislocation. Blood was collected by cardiac puncture with EDTA or lithium heparin for haematological and biochemical analysis respectively. Blood samples were centrifuged at 2000 x g for 10 min and plasma was separated. The Liver and kidney was excised, weighed and homogenized with a glass–teflon homogenizer in 0.1M Tris–HCl buffer (pH 7.5) and then centrifuged at 4000 x g for 15 min for biochemical analysis. The supernatants were immediately kept frozen until they were required for analysis.

2.3 Macroscopic Examination of Organs

Macroscopic examination of the liver and kidney was carried out immediately after sacrifice. The organs were surgically removed, blotted with absorbent paper and then weighed (absolute organ weight in grams). The relative organ weight (ROW) of each animal was then calculated as follows:

$$\text{ROW} = \frac{\text{Absolute organ weight } g}{\text{Bodyweight of rat on sacrifice day g}} \times 100$$

2.4 Determination of Glucose Concentration

The glucose concentration of the blood samples of the rats was determined by the glucose oxidase method with glucose reagent strips using ON CALL PLUS glucometer from ACON laboratories Inc. San Diego USA [14].

2.5 Haematological Analyses

The method described by Alkaladi et al. [15] was employed for the analysis of haematological parameters. These parameters included red blood cells, (RBCs), haemoglobin (Hb), packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), white blood cell (WBC), neutrophils, monocytes, lymphocytes, eosinophils, basophils and platelets.

2.6 Determination of Biochemical Parameters

The method described by Tietz et al. [16] was employed for the determination of total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), highdensity lipoprotein cholesterol (HDL-C) and triacylglycerol. The plasma activities of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were determined by the method of Reitmann and Frankel [17]. The serum alkaline phosphatase (ALP) activity was assayed according to the method described by Kind and King [18]. The total protein was estimated according to the method of Grant et al. [19]. The albumin and globulin levels were determined according to the method of Doumas et al. [20]. The urea level was estimated according to the method of Patton and Crouch [21]. The sodium, potassium and chloride levels were assayed as described by Tietz et al. [16]. The Malondialdehyde (MDA) released by lipid peroxidation was determined as thiobarbituric acid-reactive substances as described by Lushchak et al. [22].

2.7 Statistical Analysis

Experimental data were expressed as mean ± standard deviation (SD) and subjected to one – way analysis of variance (ANOVA) followed by Duncan multiple range test. Values were considered statistically significant at $P < 0.05$.

3. RESULTS

3.1 Mortality and Clinical Signs

No mortality was induced by the acute administration of $Mg(OH)_2$ nanoparticles. There were no treatment-related clinical signs such as: behavioral changes, loss of fur, bite wounds, scratch wounds, eye discharge, and scabs.

3.2 Relative Organ Weight of Liver and Kidney

The result of the relative organ weight (Fig. 2) indicated that there was no significant difference in the average relative organ weights of the liver and the kidney of the treated groups and the control group. In other words, various dose concentrations of the nanoparticle did not influence the relative organ weight of both liver and kidney of rats.

3.3 Hepatic and Renal Function Parameters

The result of serum liver and kidney function parameters of rats administered magnesium hydroxide nanoparticles is presented in Table 1. The nanoparticle induced a significant increase ($P < 0.05$) in the levels of total protein, alkaline phosphatase (ALP), aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Whereas, the concentrations of albumin, globulin, sodium, potassium, chloride and urea remained unchanged throughout at the tested doses.

The administration of the nanoparticle did not significantly alter the blood glucose of tested rats when compared with control values (Fig. 3). However, a single oral dose (1000, 2000, 4000 and 5000 mg/kg body weight) of magnesium hydroxide nanoparticles significantly increased the levels of MDA in the liver and kidney of rats (Fig. 4).

3.4 Lipid Profile

The lipid profile demonstrated that the administration of the nanoparticle in either of the doses (500, 1000, 2000, 4000 and 5000 mg/kg body weight) did not significantly alter the plasma concentrations of total cholesterol, triacylglycerides, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol (Table 2).

3.5 Hematology

The hematological investigation indicated that the the nanoparticle at the tested doses significantly increased the levels of packed cell volume (PCV), red blood cell count (RBC) and haemoglobin (Hb). The levels of neutrophils, Mean corpuscular volume (MCV) and mean

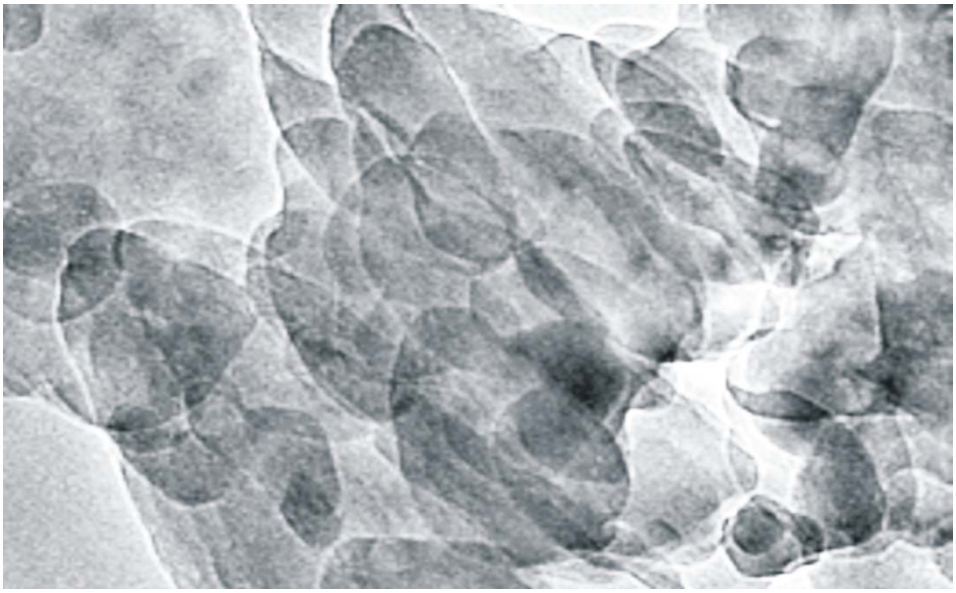

Fig. 1. The transmission electron microscope (TEM) image of magnesium hydroxide nanoparticles (www.us–nano.com)

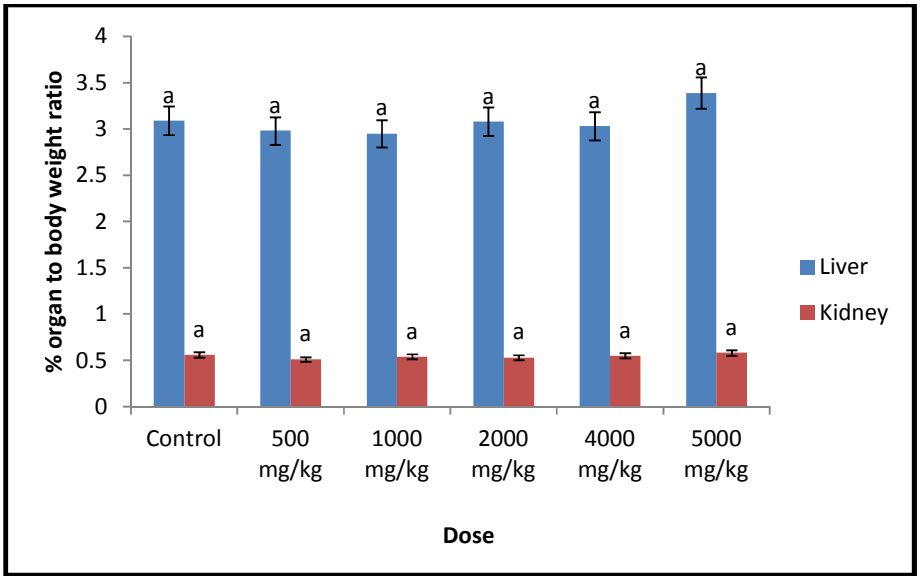

Fig. 2. Organ to body weight ratio of rats following acute doses of magnesium hydroxide nanoparticles. Results are expressed as means ± SD (n=6). Test values carrying superscript (a) are not significantly different from the control

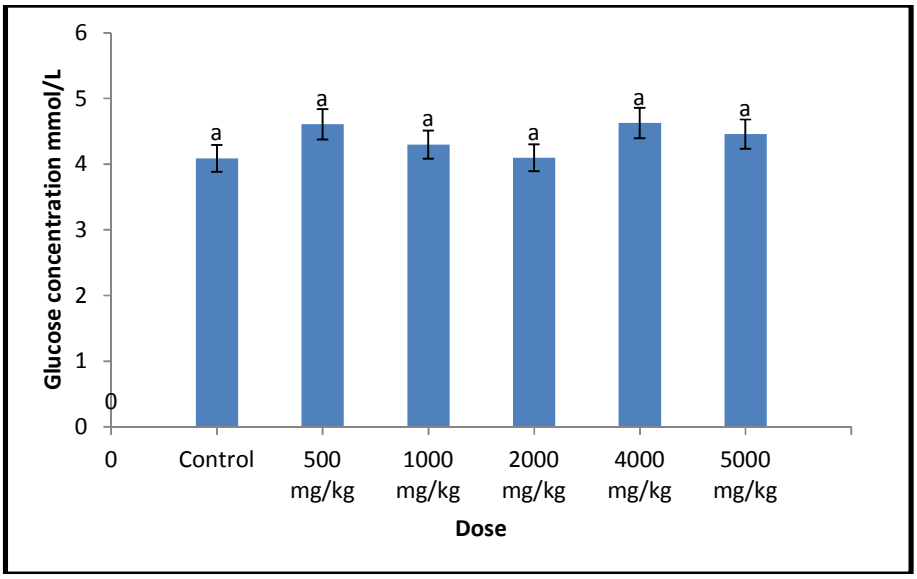

Fig. 3. Effect of acute doses of magnesium hydroxide nanoparticles on blood glucose levels of rats. Results are expressed as means ± SD (n=6). Test values carrying superscript (a) are not significantly different from the control

corpuscular haemoglobin (MCH) decreased significantly ($P < 0.05$.) after the administration of single dose of the nanopaticle. In contrast, the white blood cell count (WBC), mean corpuscular haemoglobin concentration (MCHC), monocytes, lymphocytes and eosinophils remained unaltered throughout the experimental period (Table 3).

4. DISCUSSION

The increase in the use of nanoparticles as chemotherapeutic agents has necessitated the safety evaluation of these particles. Living organisms are exposed to nanoparticles in the environment [1]. These particles tend to accumulate in vital organs in the body thereby

interfering with the functional integrity of such organs [23]. This study evaluated the effects of acute administration of $Mg(OH)_2$ NPs in rats at doses of 500, 1000, 2000, 4000 and 5000 mg/kg. A single dose of $Mg(OH)_2$ NPs neither induced mortality nor treatment related clinical symptoms in the rats even at 5000 mg/kg. The relative organ weight is a useful index of swelling, atrophy, or hypertrophy [24]. A decrease in this parameter is associated with the constriction of cells whereas; its increase is an indication of inflammation [25]. The administration of $Mg(OH)_2$ NPs did not significantly ($P < 0.05$) affect the relative organ weight of rats when compared with the control values. Biochemical markers are important indices used to monitor the adverse effects of xenobiotics [26]. Enzymes are specifically useful in assessing the functionality of organs [27]. Aminotransferases catalyze transamination reactions during amino acid metabolism. These enzymes are localized primarily in the hepatocytes. However, when the membrane integrity is compromised, the concentration of AST and ALT becomes elevated in the extracellular fluid [28]. The observed increase in the plasma activities of ALT and AST in the treated rats indicates hepatic damage as a result of altered membrane permeability [29].

Alkaline phosphatase is localized in the cells lining the biliary duct of the liver. It is a marker enzyme of the plasma membrane of the liver. The observed increase in serum ALP activities may indicate alteration in the permeability of the plasma membrane or blockage of the bile ducts [30]. The compromised integrity of the hepatobilary system is corroborated by increase total protein levels. The lack of an effect on the albumin, globulin and glucose levels observed in the experimental animals at all the tested doses suggest that secretory function of the liver was unaltered [25]. The kidney is a sensitive organ whose functioning is affected by drugs [31]. In this study, urea, sodium potassium and chloride levels were used to assess the possible renal damage due to the administration of single dose of $Mg(OH)_2$ NPs. The non significant alteration in levels of these parameters is an indication that the nanoparticle has no aggressive effects on the metabolism and the excretion of this metabolite and electrolytes in rats. The significant elevation in the concentration of malondialdehyde in the liver and kidney of experimental rats is of toxicological significance which may indicate oxidative stress [32].

Significant alterations in the lipid profile status could predispose to cardiovascular injury. An elevated level of TC, LDLC and triglycerides is associated with atherosclerosis [25]. The administration of $Mg(OH)_2$ NPs did not alter the concentration of major lipids in the rats. This is an indication that the nanoparticle did not interfere with lipid metabolism at the tested doses.

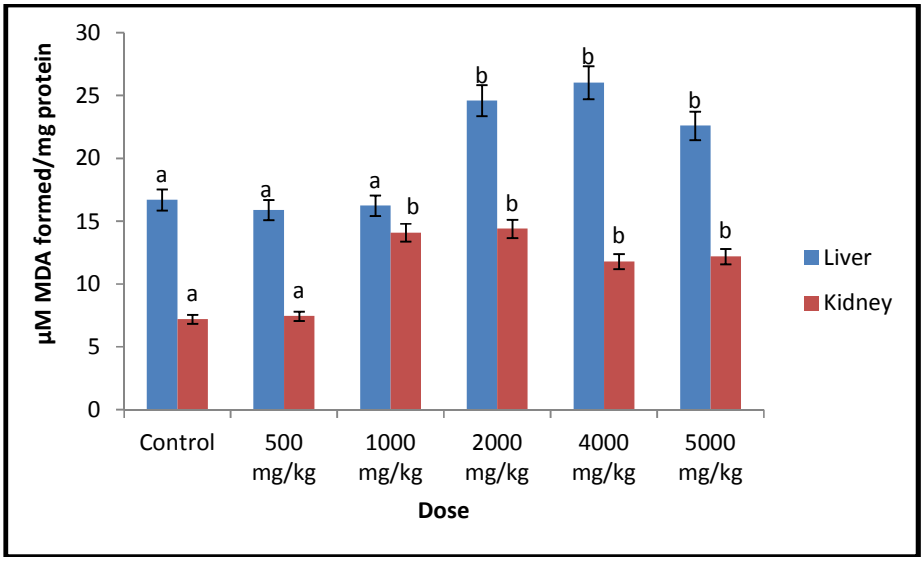

Fig. 4. Effect of acute doses of magnesium hydroxide nanoparticles on lipid peroxide levels in the liver and kidney of rats. Results are expressed as means ± SD (n=6). Test values carrying superscripts (b) are significantly different (P <0.05) from the control (a) for each parameter

Table 1. Biomarkers of hepatic and renal dysfunction in rats exposed to acute doses of magnesium hydroxide nanoparticles

Parameter	Control	500 mg/kg	1000 mg/kg	2000 mg/kg	4000 mg/kg	5000 mg/kg
Albumin (mmol/L)	32.95±3.25^{a}	38.20±1.33^{a}	36.18±2.93^{a}	36.78±2.53^{a}	34.00±4.94^{a}	38.53±5.50^{a}
Total protein (g/L)	60.17±4.69^{a}	60.30±4.87^{a}	63.96±7.97^{a}	66.57±10.62^{ab}	65.32±5.77^{ab}	74.40±7.44^{b}
Globulin (g/L)	29.38±6.83^{a}	29.52±2.60^{a}	26.09±5.51^{a}	35.68±6.60^{a}	28.37±3.28^{a}	35.87±7.03^{a}
ALP(U/L)	24.30±5.80^{a}	37.70±11.90^{bc}	38.70±4.50^{b}	34.30±7.10^{b}	39.31±7.20^{b}	45.70±3.11^{c}
ALT(U/L)	11.09±4.26^{a}	13.65±2.66^{a}	17.92±6.79^{ab}	19.01±4.93^{ab}	19.24±6.11^{ab}	27.20±8.60^{b}
AST(U/L)	38.83±4.89^{a}	79.20±18.66^{c}	67.60±19.83^{b}	74.60±13.29^{bc}	66.82±15.05^{b}	56.80±12.65^{b}
Sodium (mmol/L)	142.03 ± 1.37^{a}	142.42 ± 2.36^{a}	139.10±0.80^{a}	137.10 ± 6.52^{a}	139.80±2.21^{a}	139.60±0.80^{a}
Potassium (mmol/L)	5.79 ± 0.72^{a}	5.50 ± 0.50^{a}	5.13 ± 0.52^{a}	5.09 ± 0.34^{a}	5.06 ± 0.70^{a}	5.78 ± 0.15^{a}
Chloride (mmol/L)	109.20±1.50^{a}	111.68 ± 3.39^{a}	110.52±1.59^{a}	110.60 ± 1.22^{a}	112.32±2.46^{a}	109.05±1.94^{a}
Urea (mmol/L)	0.35±0.24^{a}	0.39±0.11^{a}	0.34±0.46^{a}	0.37±0.60^{a}	0.27±0.56^{a}	0.30±0.84^{a}

Results are expressed as means ± SD (n=6). Test values carrying superscripts (b) are significantly different (P <0.05) from the control (a) for each parameter

Table 2. Lipid profile in rats exposed to acute doses of magnesium hydroxide nanoparticles

Dose	Total cholesterol mmol/L	Triglyceride mmol/L	LDL-C mmol/L	HDL-C mmol/L
Control	1.46 ±0.31^{a}	0.53 ±0.31^{a}	1.02 ±0.41^{a}	0.29 ±0.11^{a}
500 mg/kg	1.63 ±0.11^{a}	0.38 ±0.30^{a}	1.10 ±0.18^{a}	0.23 ±0.09^{a}
1000 mg/kg	1.68 ±0.49^{a}	0.46 ±0.30^{a}	1.16 ±0.47^{a}	0.31 ±0.05^{a}
2000 mg/kg	1.58 ±0.36^{a}	0.90 ±0.36^{a}	0.91 ±0.54^{a}	0.26 ±0.06^{a}
4000 mg/kg	1.76 ±0.23^{a}	0.55 ±0.21^{a}	1.23 ±0.32^{a}	0.27 ±0.15^{a}
5000 mg/kg	1.90 ±0.10^{a}	0.70 ±0.45^{a}	1.27 ±0.26^{a}	0.34 ±0.05^{a}

Results are expressed as means ± SD (n=6). Test values carrying superscripts (b) are significantly different (P <0.05) from the control (a) for each parameter

Table 3. Effect of acute doses of magnesium hydroxide nanoparticles on heamatological parameters of rats

Parameter	Control	500 mg/kg	1000 mg/kg	2000 mg/kg	4000 mg/kg	5000 mg/kg
PCV (%)	41.00± 2.00^{a}	41.00 ± 4.00^{a}	41.00 ± 3.00^{a}	40.00 ± 2.00^{a}	43.00 ± 3.00^{b}	48.00 ± 2.00^{b}
RBC (x10^{6}µ/L)	2.70 ±0.32^{a}	6.09 ±0.76^{bc}	6.26 ±2.50^{bc}	7.06 ±1.65^{d}	5.97 ±1.30^{b}	5.67 ±1.32^{b}
WBC (x10^{3}µ/L)	5.78 ±0.26^{a}	5.63 ±0.45^{a}	5.67 ±1.37^{a}	5.93 ±0.35^{a}	5.86 ±1.24	5.20 ±1.41^{a}
Hb (g/dL)	16.05±0.94^{a}	19.17±1.61^{c}	16.92±4.16^{b}	17.33±1.04^{b}	19.38±1.11^{c}	18.00±0.71^{bc}
MCV (fL)	151.50±15.45^{a}	64.37±5.46^{c}	74.28±28.51^{bc}	51.80±1.98^{d}	80.13±18.94^{b}	82.70±11.31^{b}
MCH (pg)	61.25±4.43^{a}	31.50±6.36^{b}	30.50±11.06^{b}	25.00±2.00^{c}	32.67±9.81^{b}	31.35±4.74^{b}
MCHC (g/dL)	40.70±1.39^{a}	39.42±1.53^{a}	41.94±1.62^{a}	41.91±1.09^{a}	40.28±2.03^{a}	39.90±2.02^{a}
Neutrophils (%)	38.00±5.66^{a}	21.00±3.46^{b}	28.00±2.00^{b}	14.67±1.16^{c}	18.67±1.16^{bc}	28.00±2.02^{b}
Lymphocytes (%)	62.00±2.83^{a}	61.50±3.00^{a}	60.00±3.27^{a}	60.00±2.83^{a}	63.00±3.83^{a}	60.67±4.16^{a}
Monocytes (%)	12.00±2.45^{a}	10.00±1.27^{a}	9.67±4.51^{a}	9.63±4.16^{a}	11.20±1.79^{a}	11.00±1.41^{a}
Eosinophils (%)	5.60±1.67^{a}	5.60 ±0.89^{a}	5.00 ±2.00^{a}	6.00 ±1.41^{a}	5.80 ±1.10^{a}	5.33 ±2.31^{a}

ResResults are expressed as means ± SD (n=6). Test values carrying superscripts (b) are significantly different (P <0.05) from the control (a) for each parameter

The hematopoietic system is highly sensitive to toxic compounds. The normal range of these hematological parameters can be altered by the ingestion of xenobiotics. The parameters usually assessed are red blood cell, packed cell volume, white blood cells, hemoglobin content and differentiated leukocyte count [33]. The significant elevating effect of the nanoparticle on the RBC, PCV, Hb and MCV may be an indication that the nanoparticle stimulated the rate of production of the blood corpuscles since all these parameters are related other. It could also imply that $Mg(OH)_2$ NPs was able to stimulate the release of humoral regulator of red cells (erythropoietin) in the kidney. The non – significant effect of single dose of $Mg(OH)_2$ NPs on WBC is an indication that the rate of entrance of the haematological parameter into the blood from the bone marrow and removal from circulation is unaltered [34]. The levels of lymphocytes monocytes and eosinophils were unaltered. This implies that the nanoprticles does not pose any adverse effect on the immune system [30]. However, the reduction in the level of neutrophils will adversely affect phagocytosis in the experimental rats.

5. CONCLUSION

In conclusion, the overall result of this study clearly demonstrates that the administration of magnesium hydroxide nanoparticles did not induce major behavioral changes in rats. There were no alterations in the organ to body weight ratio and lipid profile at the tested doses. No mortality was observed as a result of exposure to the nanoparticle even at a dose of 5000 mg/kg. However, mild alterations in some hepatic functional indices were observed. Further studies are ongoing to ascertain this sign of toxicity at the subacute and chronic level.

ETHICAL APPROVAL

There is no constituted ethical committee for animal use in Ekiti State University, Ado Ekiti Nigeria, where this study was conducted. However, in the animal house of the Department of Biochemistry, any experiment involving the use of animals is monitored directly by the Head of Department and Dean of faculty of science to ensure that the guidelines for principle of laboratory animal care were followed throughout the duration of the experiment.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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