Texila International Journal of Academic Research
ISSN: 2520-3088
DOI: 10.21522/TIJAR.2014.09.04.Art002

Effects of Gadolinium-Based Contrast Agents on the Kidney, Liver, and Heart of Wistar Rats

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Abstract

The harmless potential of gadolinium-based contrast agent (GBCA) used in MRI studies was remarkable until when gadolinium was detected in the brain, bones, and skin. This study aimed to evaluate the effect of four GBCAs on the liver, heart, and kidney of Wistar rats. Twenty-five (25) male Wistar rats weighing 165-239 g were divided into 4 experimental and control groups after obtaining ethical approval from the Institutional Review Board (IRB) of the Nigerian Institute of Medical Research (NIMR). Specimens in the experimental groups received 2.5 mls / day of one GBCA and the control same normal saline through the lateral tail for 5 days consecutively / week. The Livers, Hearts and Kidneys were harvested 4 weeks following last injection. Pathohistology showed all kidney tissues exposed to Gadopentetate, 80 % to Gadodiamide, and 40 % to Dotarem and Cyclolux were inflamed. Sixty percent Gadodiamide and Doterem to the liver tissue, 50 % and 20 % to Gadopentetate and Cyclolux also inflamed. Samples exposed to Gadopentetate and Dotarem had 50 and 40 % of their heart tissue inflamed. Only those to Gadodiamide and Cyclolux were not affected. Injuries like necrosis, degeneration, and hypertrophy were also noted in all the tissues. All GBCAs were statistically significant in all tissue studied. Gadolinium-based contrast agents had a weak negative correlation with inflamed and degenerated tissues, also a weak positive correlation with hypertrophied tissue, but a moderate positive correlation with necrosis tissues of the kidney, liver, and heart.

Keywords: *Contrast agents, Heart, Histopathology, Kidney, Liver, Magnetic resonance imaging.*

Introduction

Magnetic Resonance Imaging can be used for fear that radiation exposure is a problem, such as in children and pregnant women [1]. It can as well be used when the CT scan findings are non-diagnostic [1]. A comprehensive evaluation of both morphology and function in renal disease is possible with MRI [2]. Compared with other hepatic imaging modalities, including ultrasonography (US), contrast-enhanced US, CT, and positron emission tomography-CT, it offers a more comprehensive evaluation of the liver, establishing, in many cases, an accurate tissue diagnosis [3]. The most used imaging methods for diagnosing hepatocellular carcinoma (HCC) in clinical practice are CT and MRI, with MRI more detailed compared to CT [4]. Cardiac MR is being more widely accepted, considered as "gold standard," and use for more accurate cardiac assessment such as left ventricular mass, volumes, ejection fraction, evaluation of pericardial disease, complex congenital cardiac anomalies, right ventricular dysplasia, disease

Received: 10.08.2022 ***Accepted: 10.09.2022*** ***Published on: 29.10.2022***
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of the major thoracic vessels including aortic aneurysms and dissection as its superiority over others is established [5]. Apart from the cost of MRI examinations, longer scan time, and contraindications in some patients, the anatomy images and information about patients' physiological and metabolic functions are more detailed than that of the CT [4]. The detailed diagnostic quality of an image may be achieved by the contrast agent's administration.

Tolerance to GBCAs is excellent. The tissue-specific agents do have some adverse effects, though none of them is life-threatening. Identification of nephrogenic systemic fibrosis (NSF) has forced a rethink about the liberal usage of MRI contrast agents [6, 7]. A study showed macrocyclic GBCAs to be more stable and equally safer than linear agents [8]. Studies identified GBCAs as the causative agent in NSF in a patient with impaired kidney function [9-11]. The increased kidney size in autosomal dominant polycystic kidney disease (ADPKD) is associated with the severity of renal function impairment [12], and GBCAs used during MR imaging are believed to contribute to kidney volume estimates from MR images [12]. Gadolinium-containing contrast agents (Optimark, Omniscan, Magnevist, Magnegita and Gado-MRT Ratiopharm) have been contraindicated in a high-risk patient with severe kidney problems, patients who are scheduled for or have recently received a liver transplant, and in newborn babies up to four weeks of age [9, 11, 13].

The prescribing information for all GBCAs should include elderly may be at particular risk of NSF due to the impaired ability of their kidneys to clear gadolinium from the body, no evidence to support the initiation of haemodialysis to prevent or treat NSF in patients not already undergoing haemodialysis, and the type and dose of contrast agent used should be recorded to minimize the risk of NSF with GBCAs. Body organs like the kidney and liver are known to primarily eliminate these agents; reduction in organ performance may increase the time taken for gadolinium to be retained in the body leading to high toxicity. Rogosnitzky and Branch [8] reported on FDA and EMA-approved GBCAs. They identified Gadobutrol, Gadoterate meglumine, and Gadoteridol as macrocyclic GBCAs having lower dissociation constants and are thought to be more stable, while the remaining are linear forms. [14] in their study complimented Rogosnitzky and Branch's reports with evidence in 2017 following the NSF crisis and reported macrocyclic were "safer" than linear GBCAs, despite clear evidence of differences among GBCAs of the same class. Magnetic resonance imaging contrast agents should be rapidly and substantially cleared from the body after injection and subsequently imaged to prevent chronic toxicity due to the slow deposit of dissociated free metal ions in specific tissues or organs [15]. It was earlier widely believed that GBCAs are rapidly and completely excreted from the body in an unharmed state [8], though the prevalence of allergic reactions to gadolinium is uncommon (0.07%), but higher in patients with histories of allergic reactions to iodinated contrast agents [16], evidence showed adverse side effects associated with the use of GBCAs [17, 18].

According to the Royal College of Radiologists [19], the incidence of acute or severe reactions is estimated to be 0.0025 % - 0.005 %, but major life-threatening to GBCAs is extremely rare. It was documented that GBCAs are associated with very low rate of immediate adverse events (0.06 %- 0.09 %), and most adverse events are mild and managed in the imaging department. There is no published work, to the best of the researcher's knowledge, on the effect of GBCA in the liver, kidney, and heart. We hypothesized that there are no differences in the effect of the gadolinium-based contrast agents (gadopentetate dimeglumine, Dotarem, gadodiamide and cyclolux) on the kidney, liver, and heart of Wistar rats. This study was designed to evaluate the effects of gadolinium-

based contrast agents on the kidney, liver, and heart of Wistar rats.

Materials and Methods

This experimental study, which involved 25 healthy male Wistar albino rats, was conducted at the physiology laboratory of Bayero University and histology and chemical pathology laboratories of Ysusuf Maitama Sule University, Kwanar Dawaki Campus Kano, all in Kano State, Nigeria, from January 2022 to June 2022. The health condition of the rats was only determined by thorough observations, body weight, age, and assessment. No blood or urine volume, heart rate, allergens and respiratory rate taken. This model was selected for this study owing to its smaller body size, high rate of survival, and lower tumor or lesion incidence compared to other outbreed rats. Only male animals with ages of $\geq 5 \leq 6$ weeks old were included in this study since the female hormones fluctuate during the reproductive cycle and could influence the outcome of the experiment [20], and also, they have reached maturity at this time [21, 22].

Ethical approval (IRB/21/038) for this study was sought and obtained in accordance with Nigerian animal welfare law and experimental protocols, compliance with "Guide for Care and Use of Laboratory Animals" summarized by Davidson *et al* [23] from Institutional Review Board (IRB) of the Nigerian Institute of Medical Research (NIMR), Yaba Lagos, Nigeria.

The sample size used for this study was determined using a method based on ANOVA calculations and has "E" value called the degree of freedom which must be between 10 and 20.

Where:

E= Degree of freedom ($\geq 10 \leq 20$), E= Total number of animals-Total number of groups. The study aimed at the effect of four different GBCAs on three system organs (liver, heart, and kidney) of Wistar rats. The study has five groups (four groups with each GBCA being administered and one control group).

E= (5x5)-5, E= 25-5, E=20.

The sample size for this study was reached at twenty-five (25) Wistar rats and a simple random technique was adopted to group the animals.

The data generation procedures involved using test agents (Gadopentetate dimeglumine known as magnetic (Gd-DTPA), an ionic Gd complex with a linear polyaminocarboxylic acid ligand. Gadodiamide, also known as Omniscan (Gd-DTPA-BMA), a linear, non-ionic Gd complex, Gadoterate meglumine known as doterem by Guerbet (DOTA-Gd), a macrocyclic ionic GBCA and Gadoterate meglumine known as cyclolux by Sanochemia (DOTA-Gd), also a macrocyclic ionic) and instruments (microscope and spectrophotometer). Each of the Wistar rat was assigned to either control or four other groups (n= 5 per group). The container where the animals were kept was identified and labeled groups A, B, C, D, and the control container 'group E' **(Figure 1).** The animals were in these containers, fed and observed for 14 days prior to other procedures. Each alphabet represented animals to be administered a specific GBCA. Animals in container 'E' received normal saline. Each contrast medium labeled A, B, C, D is drawn from its bottle and 2.5 mls/ day administered intravenously through the lateral tail vein to all the Wistar rat in each of the containers labeled groups A, B, C, and D for five days consecutively/ week, and the procedure continued for 4 weeks. The same is simultaneously done with saline for the container labeled group E. The animals were left to remain in each container for another 4 weeks after the last injection, and during this period, observations were made on the specimen's skins, eyes, and even if there was any casualty. Each was pinned down, being conscious, and dissected to harvest the desired organ **(Figure 2)**. No anesthesia was used in the procedure to prevent other problems with the organs. The kidney, liver, and heart tissue of each sample was harvested in sterile sample

bottles (**Plate 3),** the last day of the 8 weeks. The incineration method through licensed commercial medical waste company was used after the body parts, and carcasses of the Rats were bagged in a seal bag provided by the division of laboratory animals.

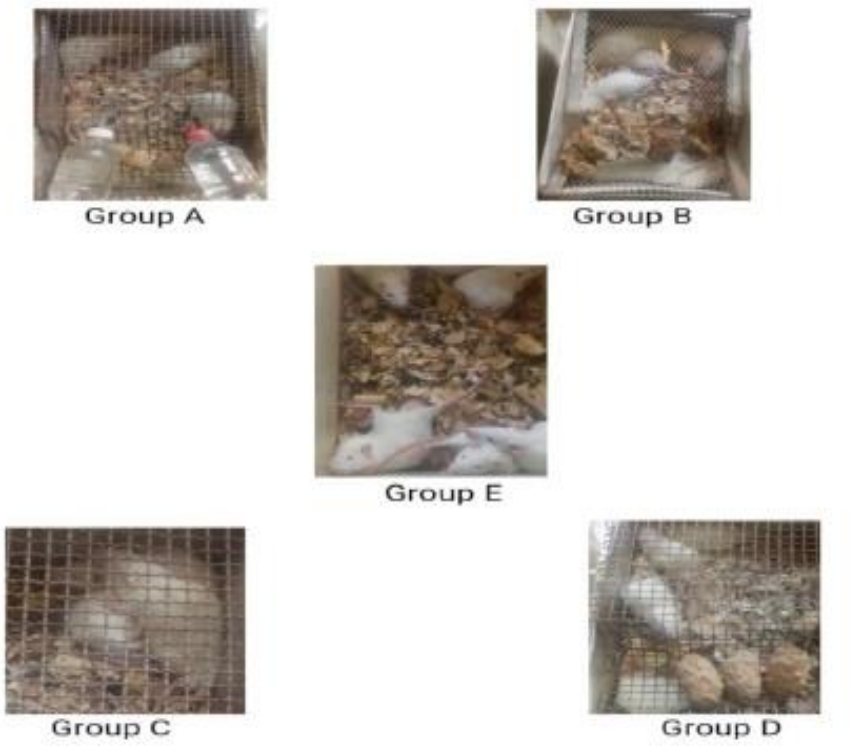

Figure 1. Male Wistar Rate in Containers

Figure 2. Wistar Rat Dissected for organ Harvesting

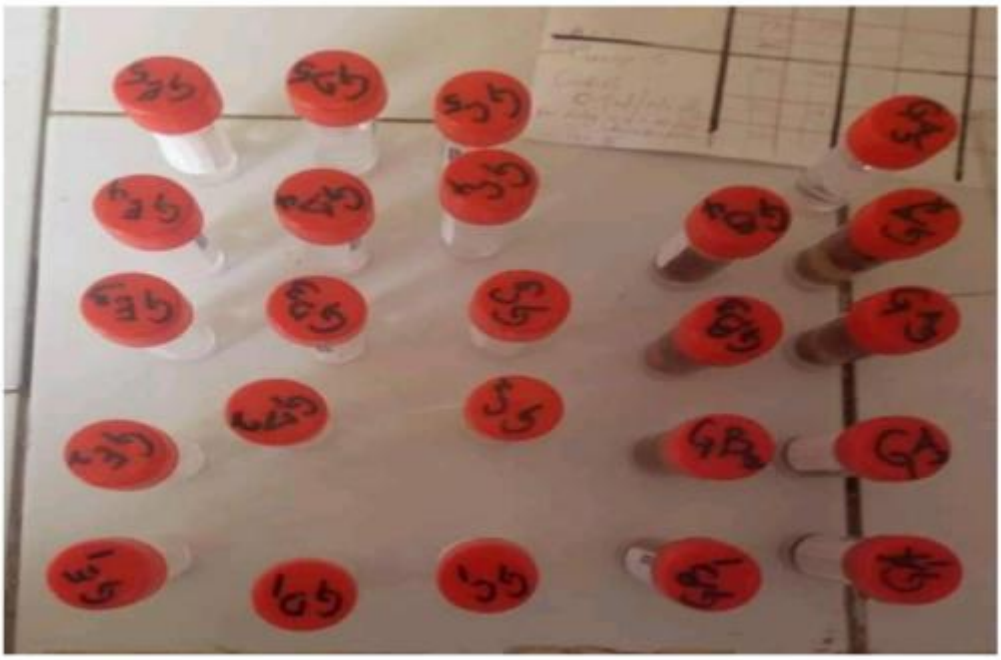

Figure 3. Labelled Sterile Sample Bottles

Potential toxicity associated with GBCAs in normal system organs in this study was tested. Acute toxicity at the injection site as well as repeated dose toxicity testing from spectrometry and histology studies were measured and documented. Careful observation was made from the period of injection of the agent to ascertain acute toxicity in all the animals as published data [24] identified skin lesions, skin thickening and cell swelling in rats. Repeated dose toxicity testing, described by Parasuraman [25], was adopted for toxicity testing. The animals received 20 intravenous injections each of 2.5 mmol GBCA per kilogram (gadolinium-exposed group) or saline (control group) over a period of 28 days (4 weeks). The animals were killed without anaesthesia. The kidney, liver, and heart tissues of each of the animals were harvested for histological changes and subjected to plasma mass spectrometry (PMS) for assessment and quantification of gadolinium retention.

The generated data were categorized into groups A, B, C, D, and E based on the type of contrast administered. The data were subjected to normality testing according to the objectives of the study and passed the normality test hence parametric method of data analysis was used. Both descriptive statistics (mean, standard deviation, and frequency) and inferential statistic (One-way analysis of variance [ANOVA]) were used for statistical analysis using the statistical package for social sciences (SPSS) software version 23(SPSS incorporated Chicago). Descriptive statistics with the mean values frequency and standard deviation documented. A one-way Analysis of variance was computed to compare the effects of the four different GBCAs on the tissues of the Kidneys, Livers, and Hearts of male Wistar Rats. The level of statistical significance was set at a p-value less than 0.05.

Results

Descriptive Statistical Information of the Sample Studied

Table 1 showed a descriptive statistic of sample's weight and length with and without tail. Average weight of the samples in all the groups with and without stood at 224.71 gram and 172.64 grams respectively. Also, the mean initial and end body length of the samples is 17.988 cm and 40.179 cm.

Table 1. Descriptive statistics: Weight and Length of the sample

Group A	**-**	**Wa (g)**	**Wb (g)**	**L a (cm)**	**Lb (cm)**
	Mean	169.75	227.75	17.200	37.625
	Std. Deviation	3.304	8.461	.8718	1.3376
	Minimum	165	217	16.5	35.7
	Maximum	172	237	18.3	38.8
	Skewness	-1.560	-.464	.676	-1.506
	Kurtosis	2.173	.028	-2.233	2.825
	N	4	4	4	4
Group B	Mean	171.60	227.00	18.640	40.420
	Std. Deviation	4.506	5.568	1.4433	2.6948
	Minimum	167	218	16.4	36.4
	Maximum	179	232	20.3	43.3
	Skewness	1.366	-1.304	-.898	-.819
	Kurtosis	2.494	1.683	1.478	.030
	N	5	5	5	5
Group C	Mean	175.20	220.40	17.800	40.820
	Std. Deviation	5.119	4.099	1.1136	2.2917
	Minimum	167	216	16.7	37.2
	Maximum	180	227	19.5	43.2
	Skewness	-1.199	1.192	1.016	-1.116
	Kurtosis	1.579	2.098	.187	1.340
	N	5	5	5	5
Group D	Mean	169.80	220.20	18.240	41.160
	Std. Deviation	1.789	9.680	1.7953	2.3437
	Minimum	167	209	15.4	37.9
	Maximum	172	231	20.3	43.8
	Skewness	-.821	-.310	-.988	-.353
	Kurtosis	2.363	-2.612	2.035	-.798
	N	5	5	5	5
Group E	Mean	173.40	228.80	17.900	40.360
	Std. Deviation	4.219	10.941	.9772	.6025
	Minimum	170	212	16.4	39.9
	Maximum	180	239	18.9	41.4
	Skewness	1.166	-1.064	-1.005	1.860
	Kurtosis	.581	.202	.465	3.688
	N	5	5	5	5
Total	Mean	172.04	224.71	17.988	40.179
	Std. Deviation	4.217	8.343	1.2756	2.2093
	Minimum	165	209	15.4	35.7
	Maximum	180	239	20.3	43.8
	Skewness	.606	-.194	-.047	-.268
	Kurtosis	-.314	-.765	-.487	-.582
	N	24	24	24	24

Wa= weight without tail, Wb= weight with tail, La= Length without tail, Lb=Length with tail, Group A=Gadopentetate dimeglumine, Group B= Gadodiamide, Group C=Dotarem, Group D=Cyclolux, Group E= Normal saline

Effect of GBCAs on the Kidney Liver and the Heart Tissues of Male Wistar Rats

Table 2 shows the presentation of the effect of GBCAs on the tissues of the kidney, liver, and heart of normal Wistar rats. A total of 72 tissues were sent for histopathology following four different GBCAs injections. Group A had 4 kidneys, 4 livers, and 4 hearts tissues harvested from samples subjected to gadopentetate dimeglumine, 12 tissue plates were examined in all, and the majority inflamed, 4 (33.33 %) were the kidney tissues, followed by 16.67 % liver and 2 heart tissue. Apart from cell increase (hypertrophy) noted in 8.3 % of the liver and heart tissues, pathohistology was experienced in all kidney tissues, 75 % of both liver and heart tissues, but 25 % of liver and heart tissue in this category were not affected by the contrast. All the tissue administered in group B contrast experienced one of necrosis, inflammation, degeneration, or hypertrophy. The kidney tissues had 60 % necrosis, 20 % hypertrophy, and 20 % cell degeneration. Inflamed livers and hearts in this group were 20 % and 80 %, respectively, a minority (20 %) of hearts and livers here had necrosis and 40 % liver cell degeneration. Groups C and D had 40 % heart tissues not affected by the agents administered. The remaining 3 hearts in group C were 20 % necrosis and 40 % inflamed, and group D 40 % hypertrophy and 20 % necrosis. The majority (60 %) of the liver tissues in group C were inflamed, and 20 % each of necrosis and hypertrophy. Hypertrophy is highest (60 %) with kidney tissue in group C, and necrosis in group D. samples administered with normal saline had no experience of any pathohistology as demonstrated in the table. Figure 4 illustrates the pathohistology plates of the Kidney, liver, and heart tissues studied.

Table 2. Histopathology of the Kidney, Liver, and Heart tissues after injection of GBCAs

Histological Features	Normal	Inflammation	Necrosis	Cell degeneration	Hypertrophy
Group A	**Gadopentetate dimeglumine (4 wistar rats)**				
Heart	1	2	0	0	1
Liver	1	2	0	0	1
Kidney	0	4	0	0	0
Group B	**Gadodiamide (5 wistar rats)**				
Heart	0	0	3	1	1
Liver	0	2	1	2	0
Kidney	0	4	1	0	0
Group C	**Dotarem (5 wistar rats)**				
Heart	0	2	0	0	3
Liver	0	3	1	0	1
Kidney	2	2	1	0	0
Group D	**Cyclolux (5 wistar rats)**				
Heart	2	0	1	0	2
Liver	0	1	2	0	2
Kidney	0	2	3	0	0
Group E	**Saline (5 wistar rats)**				

Heart	0	0	0	0	0
Liver	0	0	0	0	0
Kidney	0	0	0	0	0

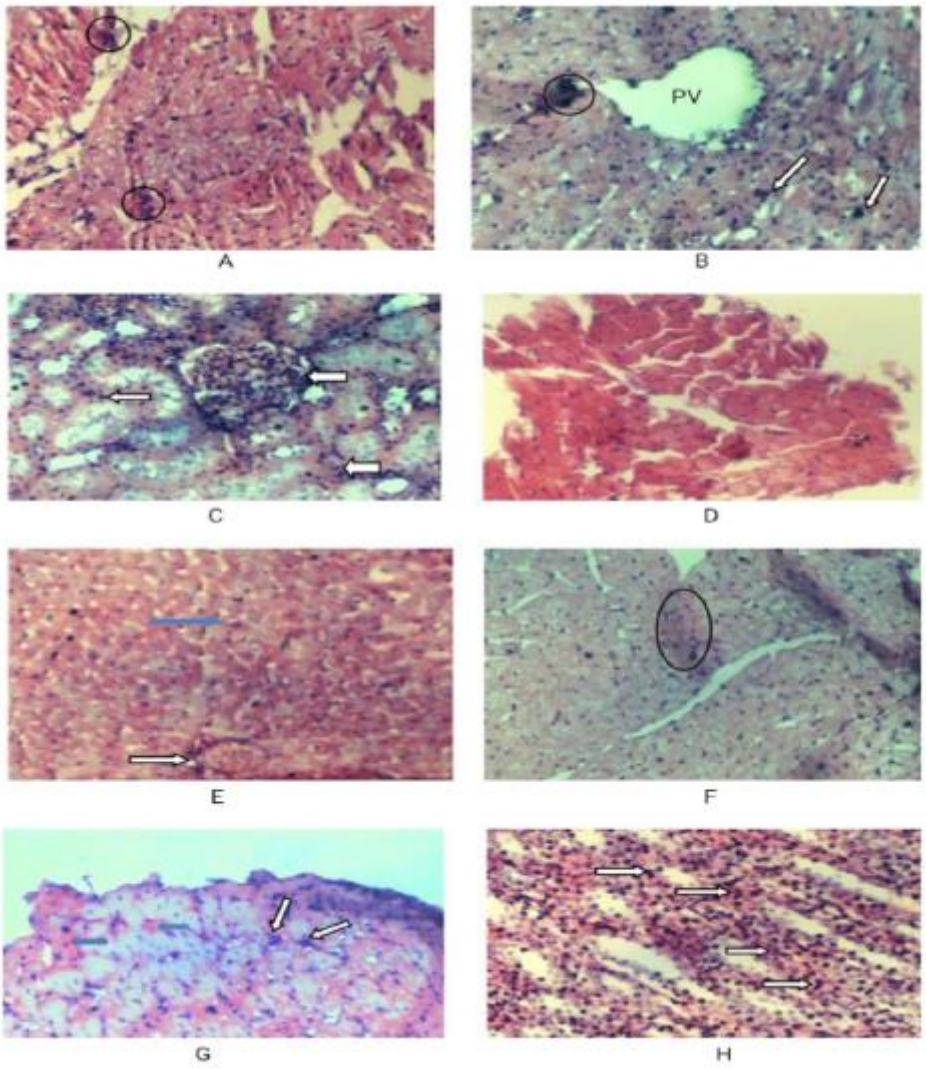

Figure 4. A-Heart Inflammation, B- Liver Inflammation Enlarged Hepathocytes, C – Nephron Inflammation, D – Heart Cell degeneration, E – Hepatocyte Ballooning Degeneration, F – Hypertropic Cardiomyopathy, G – Vascular Necrosis and Cardiomyocytes Hypertrophy, H – Kidney Cell Necrosis and Concomitant Increase in the Number of Cell

Table 3 shows the comparison of four different GBCAs on the tissues of the organs studied. The P and F values were defined. All the GBCAs were statistically significant in the kidney tissues 0.007, liver tissues < 0.001, and heart tissues < 0.001; the corresponding F-values were kidney 5.853, liver 27.658, and heart tissues 48.344.

Table 3. One-Way Analysis of Variance Comparing the Effects of the Four Different GBCAs on the Tissues of the Kidneys, Livers, and the Hearts of Male Wistar Rats

Organ	**Group**	**Mean±SD**	**F**	**P**
Kidney	Gadopentetate Dimeglumine	1.921±0.030	5.853	0.007*
	Gadodiamide	1.930±0.071		
	Dotarem	1.943±0.025		

	Cyclolux	2.054±0.075		
	Total	1.964±0.076		
Liver	Gadopentetate Dimeglumine	1.964±0.029	27.658	<0.001*
	Gadodiamide	1.880±0.113		
	Dotarem	1.745±0.034		
	Cyclolux	2.104±0.027		
	Total	1.921±0.149		
Heart	Gadopentetate Dimeglumine	2.022±0.024	48.344	<0.001*
	Gadodiamide	2.056±0.023		
	Dotarem	1.824±0.046		
	Cyclolux	1.966±0.030		
	Total	1.964±0.097		

Key: *= Significant at P<0.05

Relationship Between Four Different GBCAs Concentrations and the Histological Pattern of the Kidney, Liver, and the Heart of Male Wistar rats

Table 4 shows the relationship between all four different GBCAs concentrations and the histological patterns of the kidney, liver, and heart tissues of male Wistar rats. Pathohistology of inflammation (-0.426) showed a weak negative association between the GBCAs and this pattern, Necrosis (0.539) is moderate positive correlation, degeneration (-0.188) is a weak negative correlation, and hypertrophy (0.352) is a weak positive relationship. There was no correlation (0.098) between any of the GBCAs and the normal tissues of the kidney, liver, and the hearts.

Table 4. Pearson Product Moment Correlation showing the Relationships between Concentration of GBCAs with the Histological Pattern of the Tissue of the Kidneys, Livers, and the Hearts of Male Wistar Rats

Histological Pattern	R	P
Inflammation	-0.426	0.167
Necrosis	0.539	0.071
Degeneration	-0.188	0.559
Hypertrophy	0.352	0.262
Normal	0.098	0.763

Discussion

The effect of four different GBCAs on the tissues of the kidney, liver, and heart of Wistar rats were determined in this study. The study showed effect like inflammation, necrosis, hypertrophy, and degradation in the tissue of the kidney, liver, and heart of wistar rats when exposed to any one of gadopentetate dimenglumine, gadodiamide, dotarem, and cyclolux. This study agrees with other previous studies on accumulations of gadolinium in brain tissues but further revealed the accumulated gadolinium had effects on the tissue of the kidney, liver, and heart of wistar rats. Other studies also revealed the known behavior of gadolinium in brain tissues of rodents/ rats in previous studies [24, 26-28], including transfer to pops of fetuses affecting postnatal brain development [28] after injection of GBCAs. In some studies, accumulations of gadolinium were noticed in CSF [26], liver, skin, and bones [24, 29], also human and animal bodies [24, 29]. Macrocyclic GBCAs were previously believed to be more stable than linear (Guo *et al.*, 2018), but further review considered the possibility of macrocyclic gadolinium

deposition in human brain [29]. This current study utilized two linear (gadopentetate dimeglumine and gadodiamide), together with two macrocyclic, brands of gadoterate (dotarem and cyclolux), and was observed that all the GBCAs had deposition of gadolinium in the tissue of the organs studied as this was confirmed through the spectrophotometric readings. In general, the incidence of acute adverse reactions in previous studies [17,18] was low (1.7 %); the four studied gadolinium agents here, were only trivial, as deliberate effort was made to consider the site of injection, then the behavior and moods of the rats. No significant remark was decided.

Most of the previous studies [17, 18, 24, 29, 30] included gadopentetate dimeglumine, gadodiamide, and doterem, but only very few [31] considered cyclolux a brand of gadoterate, without clear clinical evidence existing indicated that gadolinium retention causes toxicity. [31], clarifies the rejection of both gadopentetate dimeglumine and gadodiamide in medical practice, but established the continuous use of both cyclolux and dotarem.

This study ensured the inclusion of macrocyclic GBCA, both linear ionic and non-ionic to substantiate and possibly confirm the argument by most authors [30,32-34] on the stability of macrocyclic GBCAs over linear. The former was believed to be well tolerated and has a safety profile than the latter, but this present study revealed high level of injury from all the GBCAs used as evidence in the histopathology having one of inflammation, necrosis, hypertrophy, swelling of the cells, infection and also apoptosis, this could have been due to the retention of free Gd^{+3} in the studied organs for the period (4 weeks) prior to harvesting for laboratory examinations. It was evident in the current study that most of the tissues experienced some certain level of changes weeks after exposure to the GBCAs studied. The samples exposed to gadopentetate dimeglumine had all kidneys and 50 % hearts plus 50 % livers inflamed.

The samples in this group 25 % normal histology of both the liver and the heart and 25 % liver necrosis and heart hypertrophy. Group 2, in this current study that, received gadodiamide had 80 % of the kidneys, 40 % liver, and none of the heart tissues inflamed as demonstrated in table 4. The heart tissues of those samples that received this agent had about 60 % necrosis, while cell degeneration is noticed in the liver tissue of about 40 % of these samples. All the hearts, livers, and kidneys of the samples administered gadodiamide had one injury or the other, and there was no normal histology noticed in the end. Group C and D were brands of gadoterate meglumine, their administration in their respective groups had 40 % normal kidney tissues for those that received Dotarem and same 40 % normal heart tissues for Cyclolux in group D. Sixty percent of the tissue of the livers and hearts of those that received Dotarem were inflamed and hypertrophied respectively. Also, 40 % had inflamed kidney and heart tissues. The remaining samples in group C, had 20 % hypertrophied liver tissue and 20 % liver and kidney tissue necrosis. Cyclolux in group D inflamed 40 % of the kidney and 20 % of the liver tissues. Kidney necrosis of 60 % of the samples, 40 % hypertrophy of the liver, also 40 % of liver and 20 % heart necrosis were caused by this agent. Several authors [35-39] gave similar findings on tissue with GBCAs used in this present study but were reportedly linked to impair organs. Autopsy findings already showed accumulation of Gd^{+3} in brains, bones, and skin tissue [40].

Also, [41] identified deposition of gadolinium in neuronal tissue, which was analyzed by inductive plasma mass spectroscopy, similar to the method used in the current study to detect retention of Gd^{+3} in the studied organs. This preclinical study clarified the previous confusion [42] on the effect of retained gadolinium in a patient with normal renal function and possibly heart and liver functions. The degree of damage shown from

the present results following injection of all the GBCAs indicated that the substances were no longer chelated (this substance was chelated by ligands aimed to help in its clinical use), but the Gd^{+3} from the substances (GBCAs) was released inside the sample (Wistar rats) as evidence in this study thereby accumulating in the organs [43-45].

Highest path histology seen with group A contrast is inflammation (kidney > Liver=heart) followed by hypertrophy (Liver= heart) while lowest is necrosis and cell degeneration. Inflammation is highest in group B heart > liver, followed by necrosis (kidney > liver = heart), but liver degeneration > kidney hypertrophy are the lowest in this category. This signifies that the GBCAs used in this study were very unsafe because of their toxicity. The saline concentrate recorded zero in the samples they were administered. Major and Meade [46] questioned the efficiency of chelates to completely resist Gd^{+3} dissociation from its substance, and it appears to agree with the current study.

Conclusion

Most of the tissues of the heart, liver, and kidney of the male Wistar rats were damaged by gadopentetate dimeglumine, gadodiamide, dotarem and cyclolux. This study showed there were significant statistical differences among the GBCAs used.

Histology results showed correlations between the concentration of GBCAs and histological patterns of the kidneys, livers, and hearts of male Wistar rats. Specifically, samples exposed to Gadopentetate dimenglumen, Gadodiamide, Dotarem, and Cyclolux concentrations reported more significant differences in kidneys, livers, and hearts of Wistar rats than those exposed to normal saline.

Conflict of Interest

There was no conflict of interest declared among the authors.

Acknowledgement

Dr. O. Dixon, Dr. K. Gopal, Dr. S. Mohammed, Mr. M.P. Ogolodom.

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