International Journal of Research in Medical Sciences
Ugwu AC et al. Int J Res Med Sci. 2016 May;4(5):1625-1631
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20161238

Research Article

Splenotoxic effect of radiographic developer effluent on Wistar rats

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Received: 04 March 2016
Accepted: 07 April 2016

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ABSTRACT

Background: Histological changes associated with toxicity of radiographic developer effluents on spleen tissues have not been previously studied. The present study therefore aimed at demonstrating the histopathological changes in splenic tissues of Wistar rats following exposure to developer effluent.
Methods: Eighteen young Wistar rats weighing 140-220g were used for the study. The animals were divided randomly into three groups of 6 rats each based on the dose of developer effluent administered to them – i.e. control group I (0 dose) and experimental groups II (lower dose, 200 mg/kg) and III (higher dose, 400 mg/kg) respectively. The groups were further classified as either A or B sub-groups of three rats each, depending on the duration (14 or 28 days) of effluent administration. The effluent administration was done by oral gavages.
Results: Normal spleen histology was observed in the control group. In contrast, tissue degeneration and necrosis; lymphocytic infiltration as well as reduction of splenic follicles were observed in some of the test groups (IIA, IIB and IIIA). Interestingly, the toxic effects of the developer effluent on group IIIB administered with higher dose for a longer period of 28 days were not as severe as observed in the other test groups.
Conclusions: The present study which indicated adverse effects of exposures to sub-lethal doses of developer effluent on Wistar rats' spleen tissues suggests the need for proper management and disposal of radiographic effluents.

Keywords: Environment, Exposure, Radiography, Histopathology

INTRODUCTION

The impairment of organ function is a direct consequence of alterations in the histological structures of the organ, and this may be dependent on the dose or duration of exposure to toxic substances.[1] Exposure to harmful and toxic substances is known to likely occur through the air, water that we drink, diet, from medications, the environment and workplace.[2] Radiographic developer effluent, an exhausted waste generated during radiographic processing has been reported to contain organic and inorganic substances toxic to the environment (soil, water) and food in cases where they are inappropriately disposed of.[3] Some of the components of developer effluent include hydroquinone, quinione, chlorides, carbonate ion, acetic acid, bromide ion, sulphates, sodium acetate, boric acid, methol and color.[4] The effluents are also often discarded with high chemical oxygen demand (COD) and hydrogenic potential (pH), total dissolved solids concentration and turbidity that are over allowed limits.[5] Following their discharge into the environment, these toxic substances may enter into the food chain and ultimately affect both animals and humans adversely. Unfortunately, there is no legislation on the

management of the radiographic effluents in Nigeria and other developing countries. This means that many photographic and radiographic/health centers including teaching and research institutions dispose the effluents into streams or public sewer systems without previous treatment or recycling. Of greater concern is the fact that individuals who are occupationally exposed to the effluents and the general public whose environments are polluted are unaware of the danger posed by these toxic substances.

Apart from their effects on the environment, exposure to toxic substances (acute or chronic) may also pose great danger to body organs particularly those associated with waste disposal as well as blood transport, storage and purification. There is paucity of information on the toxic effects of developer effluent on body tissues or organs. A recent study has demonstrated that acute/chronic and long-term/short-term exposures to sub-lethal doses of developer effluent may cause alterations in the histology of the heart of Wistar rats.[6] However, to the best of our knowledge, no previous study has reported toxic effects of radiographic developer effluent on splenic tissues. The spleen of living organisms is a vital organ that plays essential roles such as storage and purification of the red blood cells and removal of microbes and worn out or damaged red blood cells.[7] It is also an important organ in the immune system since it produces white blood cells and synthesizes antibodies that recognize and fight foreign pathogens and allergens.[8] Because of its role in storage and purification of blood, the spleen may be vulnerable to the development of various forms of injury if exposed to toxic substances. The present study therefore is aimed at investigating the histopathologic effects of exposure to radiographic developer effluent on the splenic tissues of Wistar rats.

METHODS

Animals

Eighteen apparently healthy Wistar rats weighing 140-220 g were used for the study. They were housed in the animal house of the Department of Human Anatomy, Nnamdi Azikiwe University, Nnewi Campus, under standard conditions (29±2^{o}C temperature, 40-55% humidity, good ventilation) and had free access to water and diet (normal rat chow). They were acclimatized for two weeks before the start of the experiment.

Test chemical

The original product, a commercially prepared developer (a chemical used in processing photographic or x-ray films) was purchased from Begood Manufacturing Company Ltd, China. The main components of the developer are hydroquinone, sodium carbonate, sodium sulfite, potassium bromide and water.[9] The content of the exhausted developer effluent, the liquid waste material generated from radiographic processing, include hydroquinone, quinione, carbonate ion, acetic acid, bromide ion, sulphates, sodium acetate, boric acid, methol and COD. It has a P^{H} of 10.4. The lethal dose (LD_{50}) concentration of the developer effluent was calculated as 2450 mg/kg body weight using the formula: $LD_{50} = \sqrt{a} \times b$ (where: a = the lowest dose that brought death i.e. 3000 and b = the highest dose that did not kill i.e. 2000). The lethal dose test of the developer effluent was carried out at the Faculty of Pharmacy and Pharmaceutical Sciences, Nnamdi Azikiwe University, Agulu Campus according to the method employed by Lorke.[10] The concentrations of the developer effluent used for the experiment were sub-lethal doses of 200mg/kg (lower dose) and 400mg/kg (higher dose) of body weight.

Experimental design

The present experiment was designed to be time and dose-dependent. The animals were divided randomly into three groups of 6 rats each based on the dose of developer effluent administered to them – i.e. control group I (0 dose); experimental group II (lower dose, 200 mg/kg) and experimental group III (higher dose, 400 mg/kg) respectively. The groups were further divided into either A or B of 3 rats each according to the duration (14 or 28 days) of effluent administration. Thus control groups IA and IB were administered with distilled water for 14 and 28 days respectively; group IIA rats were administered with lower dose (200mg/kg) of effluent for a short term period of 14 days; the group IIB rats were administered with the lower dose of effluent for a long term period of 28 days; group IIIA rats were administered with higher dose (400 mg/kg) of effluent for short term period of 14 days; and group IIIB rats were administered with higher dose of effluent for long term period of 28 days. The effluent administration was done by oral gavages. The average developer effluent consumption was 0.2 ml/day for the lower dose group and 0.42ml for the higher dose group. After 14 days, three rats from groups IA, IIA and IIIA were sacrificed (using the chloroform inhalation method), while the three rats from each of the remaining groups, IB, IIB, IIIB, were sacrificed after 28 days and their hearts harvested.

Tissue preparation

As soon as the animals were sacrificed, they were quickly dissected and their spleen removed and immediately fixed in a fixative (10% formol – saline) for 24 hours and transferred into specimen bottles, labelled and kept frozen for 48 hours before undergoing routine processing (dehydration, clearing impregnation and infiltration with melted paraffin). The spleen tissues were embedded in paraffin wax, sectioned at 3 µm placed on a hot water bath, after which they were dried and stained by Cole's hematoxylin solution and 1% eosin solution. The photomicrographs were observed using research microscope (Leica DM 750). The micrograph pictures were taken with digital camera (DCM 510.5M Pixels,

CMOS chip) connected to the microscope. All the tissue preparations and observations were done by the same research personnel.

Ethical consideration

All procedures used in this study conformed to the criteria and guiding principles for research involving animals as outlined in the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences and published by the National Institutes of Health (NIH publication 86-23 revised 1985).[11] The experiments were carried out following the ethical approval of the Ethical Board of Faculty of Health Science and Technology, College of Health Sciences, Nnamdi Azikiwe University.

Image analysis

All image processing and analyses were done using imageJ software (version 1.49). The imageJ software is a public domain, Java based image processing program designed for processing and analyzing scientific multidimentional images. The image analyses were done within the region of interest (ROI) to determine color thresholds, cell counts, total area of ROIs, and percentage area of particles, mean gray value, integrated density of gray values and shape (circularity) of objects, as summarized in the table of results. Data were expressed as means, percentages and in microns.

RESULTS

The histological findings revealed that the techniques used for tissue preparation were successful in all sacrificed rats with less technical difficulties. None of the rats died before the last day of experiment. Every histological finding or change observed and stated in this study was identified either in all the rat tissues of each group or at least in two of the three rat tissues, however, only the clearest slides were chosen.

The splenic histology of the control rats (group I) indicated normal histology of the spleen (Figure 1a). The photomicrograph reveals a normal and distinct red pulp with many cells and splenic cords as well as normal white pulp, marginal zone, central artery and normal splenic follicles. The image analysis showing the color threshold, follicle count, area of region of interest, % area of follicles within the region of interest, mean gray value, integrated density of gray values, shape (circularity) of particles, is summarized in the table of results (Table1). Results indicated that the control group had greater follicle count (n = 1869) compared to groups IIA (n = 629), group IIB (n = 1699), group IIIA (n = 650) and group IIIB (n = 939) respectively.

The splenic histology revealed significant alterations in the histological profile of group IIA (administered with 200mg/kg of effluent for 14 days) when compared to the control group. The photomicrograph indicated tissue infiltration in the red pulp (black arrow) as well as in the white pulp (white arrow). There was also tissue necrosis marked with light-blue arrows and reduction in the number of follicles (Figure 2). The image analyses in Figures 2a and 2b show that a large area of the slide was covered by large mass of distorted, degenerated tissues and infiltrates, thus accounting for the reduced number of follicles in group IIA compared to the control.

The photomicrograph (Figure 3) shows the splenic histology of group IIB rats administered with low dose (200mg/kg) administration of developer effluent for 28 days. The histological findings revealed tissue degenerations (yellow arrow), tissue infiltration (red arrow), tissue necrosis (light-blue arrow) and reduced number of follicles. The large mass of distorted, degenerated tissues and infiltrates as shown in Figures 2a and 2b, may explain the reduced number of follicles in group IIB compared to the control.

Table 1: Results of image analysis of the splenic histology in control and test groups.

Characteristics	Control (Figure 1)	Group IIA (Figure 2)	Group IIB (Figure 3)	Group IIIA (Figure 4)	Group IIIB (Figure 5)
Image color threshold	121-255	108-255	92-255	102-255	105-255
Total surface area of ROI (µ)	134,732	127, 176	136,608	71,253	103,233
Average size of ROI (µ)	72.08	202.18	80.40	109.62	109.94
Mean gray value within ROI	155.69	129.01	115.24	120.56	132.11
ID gray value within ROI (µ)	12,448.1	29,377.1	10,728.3	14,361.8	16,510.3
Follicle count within ROI	1869	629	1699	650	939
% Area of particles within ROI	28.62	27.67	28.96	15.39	21.72
Circularity of particles	0.80	0.70	0.66	0.73	0.74

The photomicrograph (Figure 4) of group IIIA rats indicated degeneration of the splenic tissues (yellow arrow), tissue necrosis (light-blue arrow) and tissue infiltration (red arrow). There was also reduction in the number of follicles compared to the control. However, the depletion of the follicles were not severe as found in groups IIA, IIB or IIIB.

Histological findings in group IIIB rats (Figure 5) indicated moderately intact red pulp with its follicles (green arrow) and white pulp with reduced number of follicles (white arrow). There was a moderate tissue degeneration (yellow arrows) and infiltration (red arrow).

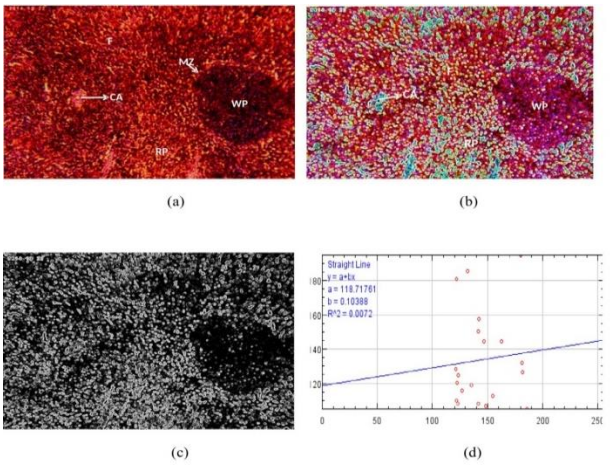

Figure 1: (a) Photomicrograph showing normal splenic histology of group I (control) rat (H and E Stain x400); The red pulp is marked with RP, white pulp is marked with WP, Marginal zone marked with MZ, the presence of central artery marked A, and splenic follicles marked with F; (b) improved image color application; (c) representative image of an analyzed field showing particles within region of interest; (d) straight line plot showing the calibration of the image intensities within the region of interest.

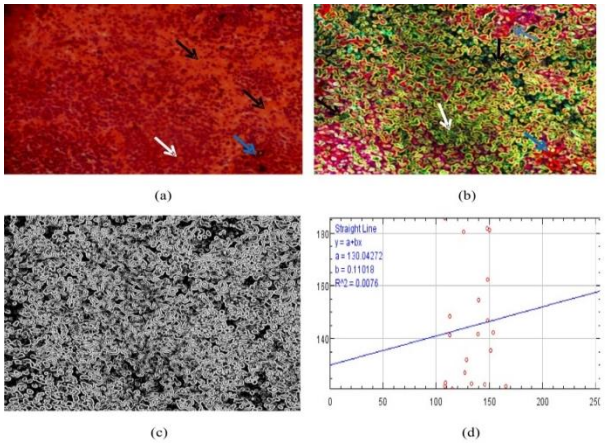

Figure 2: (a) Photomicrograph of the splenic histology of group IIA treated rat, administered with lower dose (200mg/kg) of developer effluent for a short term period of 14 days (H and E Stains x400); (b) improved image color application showing a clearer and more distinct features; (c) representative image of an analyzed field showing particles within region of interest; (d) straight line plot showing the calibration of the image intensities within the region of interest.

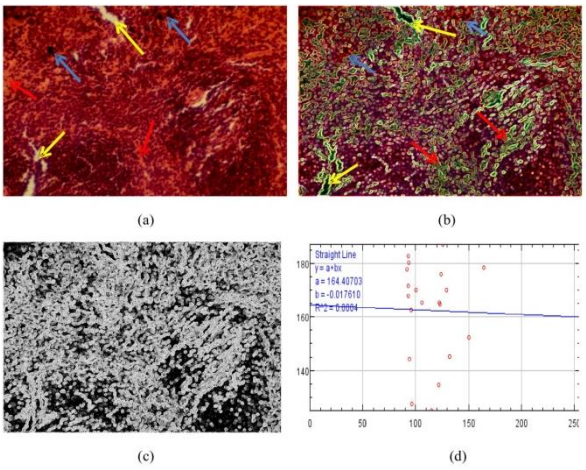

Figure 3: Photomicrograph of the splenic histology of group IIB treated rat, administered with 200mg/kg of developer effluent for a period of 28 days (H and E Stains x400); (b) improved image color application showing a clearer and more distinct features; (c) representative image of an analyzed field showing particles within region of interest; (d) straight line plot showing the calibration of the image intensities within the region of interest.

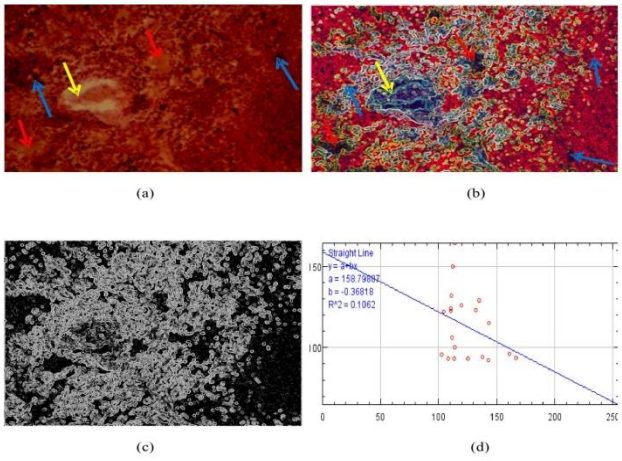

Figure 4: (a) Photomicrograph of the splenic histology of group IIIA treated rat, administered with 400mg/kg of developer effluent for a period of 14 days (H and E Stains x400); (b) Improved image color application showing a clearer and more distinct features; (c) Representative image of an analyzed field showing particles within region of interest; (d) Straight line plot showing the calibration of the image intensities within the region of interest.

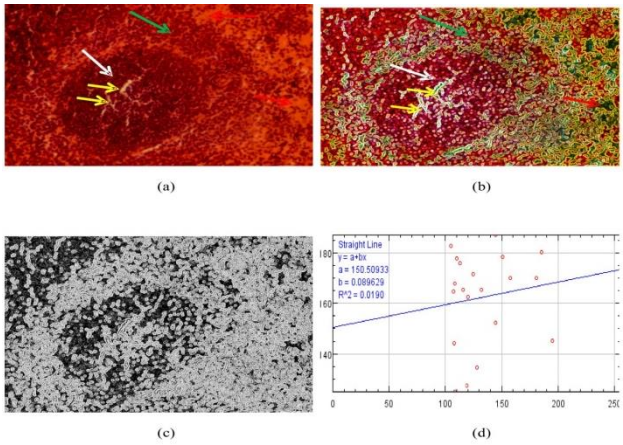

Figure 5: (a) Photomicrograph of the splenic histology of group IIIB treated rat, administered with 400mg/kg of developer effluent for a period of 28 days (H and E Stains x400); (b) improved image color application showing a clearer and more distinct features; (c) representative image of an analyzed field showing particles within region of interest; (d) straight line plot showing the calibration of the image intensities within the region of interest.

DISCUSSION

The present findings suggest that sub-lethal doses of radiographic developer effluents had toxic effects on Wistar rats' splenic tissues irrespective of dose or duration of exposure. The principal findings include: normal splenic tissues in the control group I, administered with distilled water; presence of tissue degeneration, infiltration, necrosis and reduction in the number of follicles of splenic tissues in experimental groups IIA, IIB and IIIA; moderately intact red pulp together with its follicles in group IIIB, but with evidences of moderate tissue degeneration and decrease in the number of white pulp follicles.

The spleen has been reported to be the site of direct and indirect toxicity, a target for some carcinogens, and also a site for metastatic neoplasia.[12] Many systemic or generalized diseases have splenic involvement.[12] Previous studies have also reported spleen tissue toxicity induced by chemicals.[13-16] The present study which showed tissue infiltration of the red and white pulps of the spleen is indicative of the splenic response to the toxic effects of the developer effluent. Lymphocytic as well as other leucocytic infiltrations are direct responses to infectious agents.[17] This may cause inflammation of the spleen (splenitis) and consequently result to splenomegaly.[17] Compounds inducing lymphocytes toxicity may cause necrosis of the white pulp.[12] Necrosis in the splenic white pulp is reported to be typically characterized by apoptosis of lymphocytes.[12] This may explain in part, the tissue necrosis observed in the present study.

Necrosis of the spleen simply means the death of splenic tissues and is often associated with vascular obstruction, trauma, a thrombus or neoplasia in the spleen.[18] Necrosis of splenic constituents is characterized by cell swelling, condensation and dissolution of the nucleus, and cell lysis with accumulation of abundant eosinophilic cytoplasmic and karyorrhectic nuclear debris.[18] Inflammation, hemorrhage, fibrin, fibrosis and/or mineralization may accompany splenic necrosis.[18] The present study indicated tissue degeneration and necrosis in almost all the test groups. The mechanism behind the splenic tissue degeneration and necrosis is not very clear. However, as stated above, it may partly be due to lymphocytes toxicity and apoptosis.[12] It is also possible that the cellular toxicity due to developer effluent overload may have generated free radicals which eventually caused splenic tissue damage. There has been some evidence to suggest that free radicals trigger and increase cell death mechanisms within the body such as apoptosis and in extreme cases necrosis.[19] Interestingly, a recent study has found that hydroquinone, a component of developer effluent, was able to enhance radical generation in RAW264.7 cells, suggesting its role as a strong pro-oxidant agent with chemical reactivity.[20,21] In addition, hydroquinone which is a major component of cigarette smoke has been implicated in the increased rates of higher respiratory tract infection in chronic cigarette smokers and reported to play a role in various immunotoxicological conditions.[20,22,23]

Loss of follicles may be a consequence of inflammatory, toxic, or neoplastic lesions of the spleen.[12] Inflammatory reactions of the spleen occur in the context of two pathophysiological settings.[24] First, lymphoid hyperplasia of the spleen can be the result of principally, physiological production of immune effector cells due to viral infections, autoimmune diseases, and acquired or inherited immunodeficiencies. Second, the spleen itself may be the target of a pathological inflammatory reactions of exogenous chemicals introduced into the body.[24] A previous study has shown that exposure to sub-acute boric acid, another component of developer effluent can cause dose-dependent histopathological degenerative changes in kidney tissue.[25] Another study also reported that at higher concentrations, boric acid could significantly inhibit the development of the spleen and even exhibit toxic effects.[26]

It is noteworthy that the long term administration of higher dose of developer effluent indicated moderately intact red and white pulps, improved number of follicles, absence of necrosis and only a moderate tissue degeneration and infiltration. These observations suggest a possible splenic tissue regeneration or recovery from injury with longer duration of exposure to developer effluent. It is not clear whether this is due to the intrinsic ability of the splenic tissue to recover from toxic injury or its resistance to further inflammatory responses to a toxic assault. It is also not clear if the recovery is due to dose-dependent curative effects of certain constituents of the

effluent on splenic tissues. For example, it has been proposed that hydroquinone could have potential curative effects in inflammatory disease.[27-29] In addition, hydroquinone has recently been reported to be a potent antioxidant with radical scavenging activities.[27,30] The need to understand the mechanisms behind the modest recovery of splenic tissue after exposure to a higher dosage of a potentially harmful chemical such as developer effluent calls for further studies to elucidate these facts.

Limitations of study: Cellular or tissue toxicity can be a result of direct actions of toxic chemicals or immunological responses to tissue injury. However, we could not carry out further investigations to elucidate the exact mechanisms behind the observed splenotoxic effects of developer effluent on the Wistar rats. Our major focus in this study was to ascertain if there were morphological alterations or histopathological changes in the spleen tissues of the rat due to acute or chronic developer effluent exposures. In view of the above limitation, we therefore recommend further studies to explain the exact mechanisms behind the observed histopathological changes.

CONCLUSION

The present study indicated adverse effects of acute/chronic and long-term/short-term exposures to sub-lethal doses of developer effluent on Wistar rats' splenic tissues. In view of the toxic effects of radiographic developer effluent observed in the present study and the need to minimize other environmental hazards and risks to public health, we recommend that, appropriate treatment of the effluent should be done before disposal. Similarly, the disposal of developer effluents should be carried out by companies duly licensed by the environmental agency. There is a strong need to provide increased awareness and guidance and improve the knowledge on specific regulations among professionals involved in health services which generate radiographic processing effluents. Furthermore, training courses on 'health services waste management' for different institutions should be encouraged and provided by health and environmental protection agencies.

ACKNOWLEDGEMENT

We wish to thank the Radiography Department, Nnamdi Azikiwe University, Nnewi Campus, for the support and assistance provided during the entire study. We wish to also thank the staff at the Histology Lab of Human Anatomy Department for their technical assistance. It should be noted that no financial assistance of any kind was received from any organization for the conduct of this research.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethical Committee

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Cite this article as: Ugwu AC, Dimkpa U, Agba ON, Eteudo AN, Anikeh LC, Maduka SO, et al. Splenotoxic effect of radiographic developer effluent on Wistar rats. Int J Res Med Sci 2016;4:1625-31.