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Assessment of Histologic Features of Different Tissues of Female Wistar Rats Dosed with Counterfeit Neurobion®

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Abstract
Tissue histology results still remain one of important tools used to assess the harmful effects of a xenobiotic on many organs in the field of Toxicology. Exposure to fake drug is a common occurrence in a Third World country like Nigeria. The impact of fake neurobion on tissues such brain, lung, heart and ileum is therefore being investigated. Adult female albino rats employed for the study were randomly divided into 3 groups of 6 rats per group. Rats in group 1 were treated with 30 mg/kg of fake neurobion, group 2 rats were administered with 30 mg/kg BW of genuine neurobion®, while rats in group 3 (control) received distilled water. Determination of the possible harmful effects of this agent on tissues was probed using haematoxylin and eosin (H & E) technique. The results of the study did not reveal any alteration in the histologic manifestations of all the tissues examined, as all featured no visible lesions. While these results suggest that the formulation is not toxic to cells of the brain, heart, lung and ileum it does not preclude a possible alteration of the micronutrients. It is therefore being suggested that serum micronutrients levels of rats treated with this fake neurobion be investigated.

Keywords: Histologic features; tissues; fake neurobion.

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INTRODUCTION

Intake of vitamins at the level of recommended daily allowance is essential for health, life and proper development[1]. This may not be unrelated to the diverse biochemical roles they play in a living organism. Some of these functions include hormone-like properties e.g. as regulators of mineral metabolism, as in the case of vitamin D; antioxidants property (e.g. vitamins E and C) as well as regulators of cell and tissue growth and differentiation (e.g. some types of vitamin A)[2,3]. Neurobion tablets consist of thiamine mononitrate, pyridoxal HCl, and cyanocobalamin. These three are known to play the role of co-enzymes that aid enzymes to perform their catalytic function in metabolism[2-5]. A specific example is the role of B6 in the metabolism of amino acid[6].

While the liver or kidney has always been the target organ to establish the toxicity of an agent, some chemicals are known to exert a more pronounced toxic effect on other organs than the hepato-renal axis. This is because the toxicity of an agent on a particular tissue depends on the presence of cytochrome P450s, enzymes that are variedly distributed in organs. This means that for the toxicity of an agent to be effectively assessed, its impact on a broad range of tissues must be considered[7]. Earlier studies showed that the fake vitamin preparation used for this investigation did not contain appreciable active ingredients[8] yet its administration to rats did not result in hepato-nephrotoxicity[9] but this does not preclude its adverse effects on other organs. The aim of this study therefore is to investigate the impact of fake neurobion vitamin tablets on tissues like brain, lung, heart and intestine of female Wistar rats.

MATERIALS AND METHODS

Materials: The fake neurobion used for the study was obtained from National Agency for Food and Drug Administration and Control (NAFDAC), Western region office, Ibadan. The original product was purchased from a reputable pharmacy in Osogbo.

Experimental Animals: This animal study was carried out in accordance with national and international laws and Guidelines for Care and Use of Laboratory Animals in Biomedical Research Institutes of Health (revised 1985). Adult female albino rats of average age of thirteen weeks of age were supplied by the Experimental Animal Unit of the Faculty of Veterinary Medicine, University of Ibadan, Nigeria. They were left to acclimatize for approximately two weeks prior to the take-off of the study and were kept in cages at ambient temperature of 25±2°C and a 12 h light, 12 h dark cycle. All the animals were fed with standard diets and supplied water ad libitum. There were 3 groups of 6 rats per group. Group 1 was treated with 30 mg/kg of fake neurobion while group 2 was administered with 30 mg/kg BW of original/genuine neurobion. Merck Marker (Pvt) Ltd (7, jail road Quetta), under license of Merck GaA Damstadt Germany produced the genuine drug.

Group 3 served as the control and the rats were administered with distilled water, these served as the control group. The treatment groups were exposed to their respective treatment for a period of 21 days. Drug administration took place each day (5 days per week) between 10.00 h and 12.00 h. Route of exposure was by gastric gavage.

Histopathology: Twenty-four hours after the last dose was administered approximately 1 g of sections of lung, heart, brain, and ileum was cut and fixed in 10% neutral buffered formalin. The tissue was embedded in paraffin block and cut in 5 µm sections using motorized rotary microtome. Subsequent to this, they were stained with haematoxylin and eosin (H&E), slides were then examined under compound light microscope and photographed and histopathological changes were assessed. The slides were viewed under the microscope at magnification of ×400.

RESULTS

Histologic examination of rats administered with fake neurobion resulted in no significant tissue damage as the photomicrographs of all tissues (brain, heart, lung, ileum) showed no visible lesion as presented in **Figure 1**. In addition, the photomicrographs of brain, lung, heart and ileum of rats in genuine drug administered group as well as those in the control group also featured no visible lesion as shown in **Figures 2 and 3**.

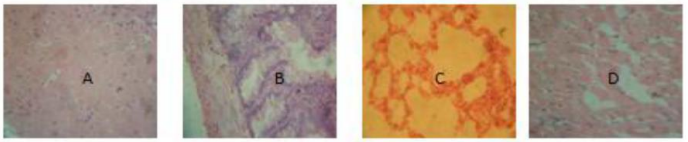

Figure 1: A- brain, B- ileum, C- lung, D- heart; all showing no visible lesion in fake neurobion administered rats

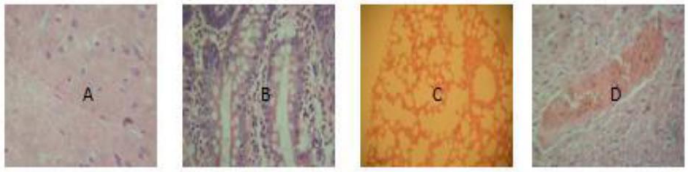

Figure 2: A- brain, B- ileum, C- lung, D- heart; all showing no visible lesion in genuine neurobion administered rats

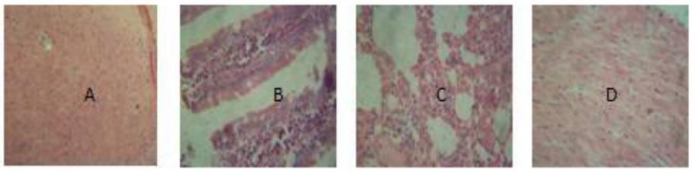

Figure 3: A- brain, B- ileum, C- lung, D- heart; all showing no visible lesion in control rats

DISCUSSION AND CONCLUSION

The need for vitamins starts from intra-uterine life, at that period they are required for normal growth and development in a multi-cellular organism[6]. Starting from the onset, the development of a fetus requires many vitamins and minerals to be present at particular times to facilitate the chemical reactions that result in formation of skin, bone, and muscle among other functions. This means that both serious and minor deficiencies can lead to, not only deficiency diseases but also permanent damage, the case of folic acid deficiency and neutral tube defect being a good example of this. While the need for vitamins in the intra-uterine life is well established, even when growth and development are completed, vitamins still remain essential nutrients for the healthy maintenance of the cells, tissues, and organs that constitute multicellular organisms. The role of some of these vitamins in enabling a multicellular life form to efficiently use chemical energy derived from food it consumes has also been revealed. This means that they help in processing or generating molecules derived from proteins, carbohydrates, and fats required for energy generation[3].

It is known that vitamins must be supplied in the diet to prevent signs of deficiency; the human body stores for different vitamins vary widely. Specifically, vitamin B12 is stored in significant amounts in the human body, mainly in the liver; the degree of storage is such that an adult human's diet may be lacking in B12 for many years before significant signs of deficiency appear. Whereas, vitamin B3 is not stored in the human body in significant amounts, such that its storage capacity is depleted only after a couple of weeks. Irrespective of the dietary source and type of storage for these vitamins, there are occasions that vitamin supplementation like neurobion may be required. And when such supplements are fake products then there is the likelihood of such agents causing significant damage to tissues.

The harmful effects of fake medicines are to be expected since even the WHO has recognized that in some cases some fake drugs contain toxins. For example, diethylene glycol contamination of paediatric related drugs is common in Nigeria[10]. Acute renal failure due to poisoning from diethylene glycol incorporation into cough syrup has been identified to be the cause of death in hundreds of patients in Haiti, Bangladesh, Nigeria, India and Argentina[11,12]. This is an example of the potentially fatal effects of counterfeit drugs containing a toxic ingredient in place of the original active ingredient. Interestingly, the brain histology results of all the rats showed no visible lesion, even rats administered with fake neurobion.

Other more specific instances whereby the devastating effects of fake drug were reported include the use of adulterated heparin imported from China in 2008 that resulted in 62 deaths in the United States[13]. Moreover, as much as 700,000 deaths annually have been linked to fake antimalarials and tuberculous agents. While about 192,000 people were reported to have died in China as a result of fake drugs in 2001; following the administration of counterfeits of meningococcal-vaccines that contained no active ingredient to 60,000 people, about 2500 people died in Niger during the 1995 meningitis epidemic[14]. Occurrences like this are leading to loss of confidence on conventional drugs and public health program by patients, especially those in the rural areas. Yet the histology of tissues such as lung, ileum and heart also revealed no visible lesions.

While experts have often regarded drug counterfeiting as a form of attempted murder, interestingly it seems no apparent damage has occurred from exposure to fake neurobion since the microphotographs of different tissues showed no visible lesion. While it may be a welcoming relief i.e. the absence of brain lung, heart and ileum damage, it seems to confirm some earlier observation that in some instances non-harmful but therapeutically non-useful ingredients are used in drug formulation. Ingredients such as talc, corn starch and baking powder have been packed into capsules for sale as therapeutic drug.

These results are not at variance with the submission of experts who often regarded drug counterfeiting as a form of attempted murder. An earlier study that determined the serum levels of this fake drug on serum micronutrient levels showed that while the levels of constituents of neurobion (thiamine mononitrate, pyridoxal HCl, and cyanocobalamin) were significantly higher in genuine drug administered rats, non-significant differences were recorded for fake drug administered rats. An indication that fake neurobion used for the study did not contain these constituents. While these results suggest that there may not be immediate danger to its consumers, it also raises the possibility of congenital abnormality in fetuses since vitamins are required from intra-uterine life as well as mismanagement of cases or conditions that require neurobion for treatment in adulthood.

This is an example of when a fake drug becomes a silent killer and why in many instances, cases of drug counterfeiting are largely over-looked and not reported to the appropriate authorities. While the histology results of no visible lesion may erroneously seem harmless, to imagine the devastating effect of incorporating baking powder in anti-glycemic drug will help us to understand the devastating effects of using non-therapeutically useful but otherwise edible and non-harmful ingredient in some other drug

formulations. Economic impact of drug counterfeiting on many nations and countries is also enormous[15] and it seems to be increasing annually. According to the WHO, not less than 32 billion US dollars were lost to drug counterfeiting business in 2004[16], with this increasing to 40 billion US dollars in 2006 and might have soared to 75 billion US dollars in 2010[16,17]. It is also known that a number of pharmaceutical companies are being deprived of their rightful profits due to the unjust competition from counterfeiters and have even resulted in the collapse of some of the companies.

As a result of such enormous economic impact, it is being advised that the methods adopted in the developed world in curtailing fake drug manufacturing and distribution should be employed by the developing countries to bring the problem to a minimal level. In addition, to prevent such effects associated with fake drug consumption, it may be necessary to address some specific major causes of widespread drug counterfeiting peculiar to the developing world like corruption, inadequate technology for protection of the identity of genuine drugs and lack of vigilance and advocacy by the healthcare providers as well as lack of political will. As Chika et al.[18] have pointed out combating the menace of fake drug will require both local and international efforts. No stone should be left unturned because drug counterfeiting results in therapeutic failure, drug resistance, economic sabotage and in some cases death. What is worrisome is that the business of fake drugs is a very lucrative and is increasing annually worldwide.

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