Asian Journal of Pharmaceutical Technology & Innovation
ISSN: 2347-8810

Research Article

Received on: 13-01-2014

Accepted on: 21-06-2014

Published on: 15-10-2014

Corresponding Author:

Ayobola A Iyanda*

*[1]Department of Chemical Pathology, College of Health Sciences, Ladoke Akintola University of Technology, Osogbo, Nigeria.

Tel: +2347039407465

*Email Id- lapeiyanda@yahoo.com

Assessment of Select Heavy Metals In Serum of Wistar Rats Administered with Fake Paracetamol Syrup

Ayobola A Iyanda*

ABSTRACT

A number of chemical adulterants or contaminants have been identified in paracetamol syrup in Nigeria, one of the most common ones being diethylene glycol. The presence of heavy metals in therapeutic preparations has also been reported in other parts of the world, with devastating consequences. The aim of this experimental work is to investigate the level of Cd, Pb, Al, Si, Ni, As, in the serum of rats administered with fake paracetamol syrup. Twenty-one female rats of average weight of 200 g were randomly divided into 3 groups of 7 rats each. Treatment lasted 21 days and the route of administration was by gastric gavage. The first group received 90 mg/kg of fake Bonadabe paracetamol, the second group was administered with 90 mg/kg BW of genuine Bonadabe® paracetamol and the third group served as the control. Statistical analysis of data obtained using analysis of variance (ANOVA) showed there were no significant differences in the serum levels of all the heavy metals investigated at $p>0.05$. Results of this study suggest that heavy metal contamination of pediatric drugs may not be common in Nigeria, although such contaminations have been reported for other preparations in some parts of the world.

Key-words: Heavy metals, Wistar rats, fake paracetamol syrup.

Cite this article as:
Ayobola A Iyanda; Assessment of Select Heavy Metals In Serum of Wistar Rats Administered with Fake Paracetamol Syrup, Asian Journal of Pharmaceutical Technology & Innovation, 02 (08); 2014.

[1]Department of Chemical Pathology, College of Health Sciences, Ladoke Akintola University of Technology, Osogbo, Nigeria.

INTRODUCTION

The devastating effectof counterfeit drugs is not limited to the developing world; according to ten Ham[1] data are available to suggest the presence of fake medicines on the marketseven in Europe. Moreover, it has also been reported that an estimated 5% of all world trade in branded goods is counterfeit, leading to huge financial losses to the pharmaceutical industry as well as a great health risk to the consumers[2-5]. Although drug has been a part of human experience from the beginning, but the regulation during that period was through social sanctions and responses to intoxication rather than sanctions for use. Even in a developed nation like the United States of Americawhere official proclamations against the use of various substances have existed for centuries, such laws were initially targeted against consumption of items like coffee, alcohol, tobacco, etc.

It was not until 1938 that a more refined means of medicinal drug control occurred when sulfa (sulfanilamide) drugs commonly used as antibiotics was introduced. Since it was not in liquid form, sulfanilamide could not be administered easily. To circumvent that problem it was dissolved in diethylene glycol but the suspension so produced was found to cause kidney poisoning that resulted in the death of 105 people in 1937. This incidence resulted in 1938 Act which states that drugs or cosmetics had to be tested for toxicity before marketing[6]. Apart from this, adequate directions for use were also required to be on package. It was the first Act that implied "use by instruction from physician only"-- in other words, the idea of prescription vs. non-prescription medicine was introduced. In addition to the existing laws, in 1962, subsequent to the thalidomide episode, amendments were added stating that a drug had to be effective for what it was intended and that approval had to be obtained before trials on humans could be conducted. All those laws have been enacted to prevent damaging effects of drugs.

Fake drugs do not meet the requirements of these laws, since the aim of their manufacturers is to make exorbitant gain; which may necessitate usage of substandard chemicals in drug formulations. And since many fake drugs in the past have been described to be contaminated with a variety of chemicals, the aim of this study is to evaluate the levels of select heavy metals in serum of rats administered with fake paracetamol syrup.

MATERIALS AND METHODS

Experimental Animals:

The animals used for the study consisted of female albino rats of average weight of 200 g purchased from the Experimental Animal Unit of the Faculty of Veterinary Medicine of the University of Ibadan, Nigeria. The animals were left in their respective cages to acclimatize for about a period of two weeks prior to commencement of the experiment. Animals were kept in cages at ambient temperature of 25±2°C and a 12 h light; 12 h dark cycle and were fed standard laboratory chow and given unrestricted access to water. Twenty-one rats were divided into 3 groups; each group comprised of 7 rats. For each of the rats, the route of administration was by gastric gavage.

The first group of rats was administered with 90 mg/kg BW of fake Bonadabe paracetamol as described by Mantzke and Brambrink[7]; rats in the second group received genuine Bonadabe® paracetamol (manufactured in Nigeria) of the same dosage and the third group served as the control and were administered with distilled water. While the fake Bonadabe paracetamol used for the study was obtained from NAFDAC, Western region office in Ibadan, the genuine product was purchased from a reputable Pharmacy. The duration of the experiment was for a period of 21 days. This study was carried out in compliance with national and international laws and Guidelines for Care and Use of Laboratory Animals in Biomedical Research Institutes of Health (revised 1985).

Preparation of serum samples & heavy metal estimation

At the end of the period of drug administration, blood was drawn from each rat by retro-orbital bleeding and introduced into an anticoagulant free bottle. The blood samples were centrifuged at 3000 g after which serum was separated and stored at -20 ºC. Levels of aluminum, silicon, cadmium, lead, arsenic, and nickelin serum were determined by the atomic absorption spectrometric method using Buck Scientific 205 Atomic Absorption (East Norwalk, Connecticut, USA).

RESULTS

Using ANOVA administration of fake and genuine paracetamol syrup did not result in significant differences in the levels of all the heavy metals estimated i.e. the serum concentrations of arsenic, aluminum, cadmium, silicon, nickel, and lead were comparable and not significantly different. All the results are presented in **Table 1.**

Table 1:Serum levels of select heavy metals in fake and original paracetamol syrup-administered rats.

	Pb (µg/L)	As (ng/mL)	Cd (mg/dl)	Si (µg/L)	Al (µg/L)	Ni (µg/dL)
Control	0.12±0.02	0.003±0.001	0.005±0.001	0.13±0.05	0.09±0.03	0.13±0.03
Fake paracetamol syrup	012±0.02	0.004±0.001	0.005±0.001	0.14±0.02	0.10±0.01	0.12±0.04
Original paracetamol syrup	0.12±0.03	0.004±0.002	0.006±0.002	0.15±0.03	0.11±0.03	0.13±0.03
F-value	0.082	0.139	0.231	0.630	1.194	2.339
P-value	0.921	0.871	0.796	0.544	0.326	0.125

Results are expressed as mean ± standard deviation. P<0.05 is significant using ANOVA. N = 7.

DISCUSSION

Heavy metals such as Pb, and Cd are elements with high molecular weight that though are sometimes found in the body at very low levels, do not play any known physiologic role. This is contrary to essential trace elements which are known for their roles as cofactors in many important metabolic processes. Sources of heavy metal exposure include food, air and water, unlike essential trace elements which are required for life, health and development, the presence of heavy metals in the body may trigger processes that may result in pathology since they hamper or derail important chemical reactions[8,9].

Arsenic is a naturally occurring element that is recognized as a human poison. It affects the activities of mitochondrial enzymes, impairs the cellular respiration, and causes cellular toxicity[10,11]. Its role in overproduction or ineffective elimination of ROS that can trigger oxidative stress thereby causing damage to all types of molecules such as proteins, lipids, and nucleic acids has been observed [12]. Therefore, its association with lipid peroxidation in the liver, kidney, and heart has been documented. Long-term exposure to elevated levels of inorganic arsenic in drinkingwater has been identified to causeskin, lung, liver, and bladder cancers as well as malignant neoplasms, diabetes, and vascular diseases[13]. Cadmium (Cd), a very toxic heavy metal and an important environmental pollutant, causes poisoning in various tissues of humans and animals[14, 15]. Its toxic effects are: inhibition of liver metabolic enzyme systems containing sulphydryl groups and uncoupling of oxidative phosphorylation in mitochondria[16], this leads to elevation in lipid peroxidation, hepatic congestion, ischemia and hypoxia[17]. Cadmium induced oxidative stress linked with liver damage is well known. These two are examples of heavy metals that their harmful effects on the body have been well documented.

Therapeutic drugs in most cases are foreign to the body; therefore they are metabolized by organs such as kidney and liver. For this reason, inter-individual response to xenobiotics even drugs that are legitimate pharmaceuticals may occur, which means they sometimes have side effects but with counterfeit medicines though, these adverse effects are more likely to occur since in some cases counterfeit drug are known to contain toxins. Many of the signs of counterfeit drugs range from allergic reactions to gastrointestinal disturbances like nausea, vomiting and diarrhea. In cases of heavy metals and toxic compounds contamination of therapeutic drug,more severe symptoms of poisoning like changes in heart function, blood glucose levels, gas perfusion (transport of oxygen and carbon dioxide in the blood), dyspnea and even organ failure may be observed. In many patients with a chronic exposure,exacerbation of the signs and symptoms of heavy metal toxicity may begin to manifest.

Heavy metal contamination of therapeutic drug is possible because of the unhygienic environment in which therapeutic agents are manufactured. For example, Parfitt[18] reported that in the 1990s many fake drugs in Russia were produced in basements and backrooms. Aside this in November 2009 in the United States of America, during a national crackdown on drug counterfeiters, 800 packages of alleged fake or suspicious prescription drugs (including Viagra for erectile dysfunction), Vicodin (a pain reliever), and Claritin (an anti-histamine) were uncovered leading to the closure of 68 allegedly unauthorized online pharmacies. Some of the drugs had as much as three times the amount of active ingredients than is typically prescribed; others contained none at all while a few contained harmful substances like drywall material, antifreeze and yellow highway paint[19].

Even with this background knowledge, the analysis of serum samples of rats treated with fake paracetamol did notresult in abnormality in heavy metal metabolism. Using ANOVA the serum levels of aluminum, silicon, cadmium, lead, arsenic, and nickel were not significantly different. This simply suggests that while heavy metals contamination of therapeutic drugs has been reported, these results do not suggest heavy metal contamination of bonababe paracetamol syrup used for this study. Even then absence of Al, Cd, Pb, Ni, Si and Asin the syrup does not preclude the ability of this fake drug to induce damaging effects.

CONCLUSION

Therefore, it is being suggested that a more exhaustive analysis of serum as well as histopathological investigation of different tissuesbe carried out to further probe a possible harmful effects of this fake product.

ACKNOWLEDMENTS*: To Mrs. V. B. Adekoya, Mr. J. O. Agbokhade and Mr. C. O. Chamuo of the Experimental Animal Unit of the Faculty of Veterinary Medicine, University of Ibadan, I acknowledge your assistance in the care of the experimental animals.*

REFERENCES

1. Ham M. Health risks of counterfeit pharmaceuticals. Drug Saf26(14), 991-7, 2003.
2. Chika A, Bello SO, Jimoh AO, Umar MT. Menace of fake drugs: Consequences, causes and possible solution. ResJMed Sci 5(5), 257-261, 2011.
3. Buowari OV. Fake and counterfeit drug: a review. Afrimedic Journal 2012; 3(2): 1-4.
4. World Health Organization (2003). General information on counterfeit medicines, http://www.who.int/medicines/services/counterfeit/overview.ht m, 28 July 2010
5. Wertheimer AI, Wang PG. (2012) Counterfeit Medicines; Policy, Economics and Countermeasures, ISBN-10: 1906799083 | ISBN-13: 978-1906799083 | Volume 1.
6. Hanif M, Ronan A, Donovan JJ. Fatal renal damage caused by ethylene glycol in paracetamol elixir: the Bangladesh epidemic. BMJ 311, 88, 1995.
7. Mantzke US, Brambrink AM. Paracetamol in childhood. Current state of knowledge and indication for a rational approach to postoperative analgesia. Anaesthesist 51(9), 735-46, 2002.
8. Ramesh B, Satakopan VN. Antioxidant Activities of Hydroalcoholic Extract of Ocimum sanctum Against Cadmium Induced Toxicity in Rats. Indian J Clin Biochem 2010 July; 25(3), 307–310.
9. Ognjanovic BI, Pavlovic SZ, Maleti SD, Zikic AS, Stajn ZS, Radojicic RM, Saicic ZS, Petrovic VM. Protective influence of Vitamin E on antioxidant defense system in the blood of rats treated with cadmium. Physiol Res52, 563–570, 2003.
10. Ranft U, Miskovic P, Pesch B, Jakubis M, Nieuwenhuijsen MJ. EXPASCAN study group Association between arsenic exposure from a coal burning power plant and urinary arsenic concentrations in prievidza district. Slovakia. Environ Health Perspect 111, 864–9, 2003.
11. Roy M, Pandey PK, Roy S, Chauhan HV. Arsenic induced haematobiochemical and histopathological alterations and its level in certain biological samples. Toxicol Int 25:57–62, 2008.
12. Droge W. Free radicals in the physiological control of cell function. Physiol Rev 82:47–95, 2002.
13. Chen CJ, Hsueh YM, Lai MS, Shyu MP, Chen SY, Wu MM, et al. Increased prevalence of hypertension and long-term arsenic exposure. Hypertension 25, 53–60, 1995.
14. Swiergosz R, Zaurzewska M, Sawicka-Kapusta K, Bacia K, Jankowska I. Accumulation of cadmium and its effect on bank vole tissues after chronic exposure. Ecotoxicol Environ Saf 41:130–136, 1998. doi: 10.1006/eesa.1998.1677.
15. Stohs SJ, Bagachi D, Hassoun E, Baguchi M. Oxidative mechanisms in the toxicity of chromium and cadmium ions. J Environ Pathol Toxicol Oncol 19, 201–213, 2000.
16. Williams F, Robertson R, Roworth M. Detailed profile of 25 major organic and inorganic substances. Glasgow: SCEIH; 1999. pp. 12–19.
17. Habeebu SS, Liu J, Klaassen CD. Cadmium induced apoptosis in mouse liver. Toxicol Appl Pharmacol 149(2), 203–209, 1998. doi: 10.1006/taap.1997.8334.
18. Parfitt, Tom. Russia Cracks Down on Counterfeit Drugs. The Lancet 368:9546, 1481-1482, 2006.
19. Mui, Ylan Q. Crackdown Targets Counterfeit Drugs. The Washington Post (Nov 20 2009), available at http://www.washingtonpost.com/wpdyn/content/article/2009/11/19/AR2009111904229.html (accessed Mar 5 2010).