



DETERMINATION OF LEAD IN PARACETAMOL ORAL LIQUID DOSAGE FORMULATIONS IN NIGERIA

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ABSTRACT

Lead is an accumulative poison. It is more harmful to children because it can affect their developing nerves and brains even at very low blood lead concentration level. This study seeks to determine the concentration of lead in paracetamol oral liquid dosage formulation. Twenty different brands of paracetamol oral liquid dosage formulation were assayed. Qualitative analysis was carried out using standard chemical test while quantitative analysis was done using atomic absorption spectrometry. Lead was detected as lead chromate in 7 (35%) brands of paracetamol oral liquid formulations. Lead concentrations ranging from 0.006 mg/l to 0.524 mg/l were detected. Since, there is no known safe blood lead concentration level in children, reduction to exposure, is important.

KEYWORDS- Paracetamol, Lead, Spectroscopic Analysis, Safety of Pharmaceuticals, Heavy metal toxicity

INTRODUCTION

Lead is a bluish-gray heavy metal with low melting point. It is a strong systemic poison. In 2009, hundreds of children in Zamfara state, Nigeria, died from exposure to lead [1-2]. According to the Institute of chartered chemists of Nigeria, several deaths have resulted from exposure to lead from illegal gold mining and contaminated homes [3].

High lead levels can cause encephalopathy, while chronic and repeated exposure may lead to, delayed sexual maturation, impaired nervous system development, neurobehavioral effects, increased blood pressure, depressed renal glomerular filtration rate, and inhibition of pathways of heme synthesis [4]. Lead is much more harmful to children than adults because it can affect their developing nerves and brains. New evidence suggests that even very low blood lead levels can be associated with neurologic

injury [5-7]. Lead has no known biological role. It is toxic, teratogenic and carcinogenic [8-10].

The lead limit for pharmaceutical products, according to the U.S. Pharmacopoeia is 10 ppm, with a daily limit of less than 10 microgram/day and less than 0.14 microgram/kg/body weight/day [11]. The standard elevated blood level for adults is 25 microgram/dl. Since children are more sensitive to the health effects of lead, no safe blood lead level in children has been determined. According to the recommendation of The U.S. centers for disease control and prevention, community-wide preventive actions are recommended when children are found to have blood lead levels greater than 10 µg/dL [4].

Atmospheric Lead contaminations have been reported in industrial area of Lagos and Ogun state [12]. Manufacturing facilities and ingredients used in the production of pharmaceutical formulations are common sources of lead contamination [13]. In an

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earlier work, we discovered that pharmaceuticals could be contaminated with lead [14]. Since children are reported to be at greater risk of lead poisoning, we decided to investigate the presence and concentration of lead in paracetamol oral liquid formulations marketed in Nigeria.

MATERIALS AND METHODS

Materials

Paracetamol syrup and suspension of different brands were purchased from pharmacies in Benin City, Abuja and Kano. The reagents used include potassium chromate, hydrochloric acid, perchloric acid, acetic acid and nitric acid. Atomic absorption spectrometer with model number AAS MODEL-SOLAAR 969 UNICAM was used for the quantitative analysis of lead. The flame used was air-acetylene flame

QUALITATIVE ASSAY OF LEAD

To 5 ml of the syrup was added 1.5 ml of 6 M hydrochloric acid (HCl) in a test tube. It was shaken, observed for the formation of white precipitate, centrifuged for one minute and allowed to stand for about five minute. The supernatant was decanted.

Hot distilled water (1 ml) was added to the solid precipitate. This was centrifuged while hot and filtered. Acetic acid and 1 M K₂CrO₄ (3 drops each) were added to the filtrate and then observed for the formation of yellow precipitate. It was centrifuged again. The presence of yellow sediments confirms the presence of lead (Pb²⁺) [15].

QUANTITATIVE ANALYSIS OF LEAD

The quantitative analysis of lead was carried out in two stages; first, digestion of the sample was done using strong acids. 1 g of the sample was weighed. 2 ml of concentrated nitric acid, 2ml hydrochloric acid and 3 ml perchloric acid were added. It was heated to almost dryness then 25 ml of distilled water was added and reheated until a clear solution was obtained. The solution was then allowed to cool. It was filtered and transferred to a 100 ml volumetric flask and made up to volume with distilled water.

The second stage is the actual analysis of the digested sample using atomic absorption spectrometer model AAS MODEL-SOLAAR 969 UNICAM

TABLE 1: QUALITATIVE ANALYSIS OF LEAD IN DIFFERENT BRANDS OF PARACETAMOL LIQUID ORAL FORMULATIONS

SAMPLE CODE	SAMPLE COLOUR REACTION WITH POTASSIUM CHROMATE		OBSERVATION AFTER CENTRIFUGATION	INFERENCE
	BEFORE	AFTER		
PS1	Pink	Yellow to dark brown	Precipitate present	Lead detected
PS 2	Pink	yellow to dark brown	No visible precipitate	Lead not detected
PE3	Light Pink	Yellow to dark brown	No visible precipitate	lead not detected
PS4	Pink	Yellow to dark brown	No visible precipitate	Lead not detected
PS5	Pink	Yellow to dark brown	No visible precipitate	Lead not detected
PS6	Pink	Yellow to dark brown	Precipitate Present	Lead detected
PS7	Light pink	Yellow to dark brown	No visible precipitate	Lead not detected
PS 8	Pink	Yellow to dark brown	No visible precipitate	Lead not detected
PS9	Light pink	Yellow to dark born	No visible precipitate	Lead not detected
PS 10	Light pink	Yellow to dark brown	Precipitate Present	Lead detected
PS11	Pink	Yellow to brown	No visible precipitate	Lead not detected
PS12	Pink	Yellow to light brown	Precipitate Present	Lead detected
PS13	Light pink	Orange to dark brown	No visible precipitate	Lead not detected
PS 14	Pink	Yellow to dark brown	Precipitate Present	Lead detected
PS 15	Colourless	Yellow to dark brown	Precipitate Present	Lead detected
PS16	Pink	Yellow to dark brown	No visible precipitate	Lead not detected
PS17	Pink	Yellow to dark brown	No visible precipitate	Lead not detected
PS 18	Pink	Yellow to dark brown	No visible precipitate	Lead not detected
PS 19	Pink	Yellow to light brown	Precipitate Present	Lead detected
PS 20	Pink	Yellow to brown	No visible precipitate	Lead not detected

The spectrometer was first calibrated using distilled water at zero concentration and standard lead solution of known concentration of 1, 2, 3, 4, 5, 6, ppm prepared from 100 ppm stock solution were used to obtain a calibration curve of absorbance against concentration at 217 nm. The absorbance of the digested sample was determined

RESULTS

The results for the qualitative and quantitative analysis of lead in different brands of paracetamol

liquid oral formulations are summarized in Table 1 and 2. Lead was detected as lead chromate in seven (7) brands (35%) in the qualitative determination of lead in form of dark brown sediment on centrifugation. Lead concentrations ranging from 0.006 mg/l to 0.524 mg/l were detected in all of the twenty (20) brands (100%) in the quantitative analysis of lead using atomic absorption spectrometer model AAS MODEL-SOLAAR 969 UNICAM™.

TABLE 2: QUANTITATIVE ASSAY OF LEAD

SAMPLE CODE	QUANTITY OF LEAD PRESENT (mg/L)	TOTAL AMOUNT OF LEAD PER DAY FOR 1YEAR OLD (10 kg) CHILD (mg)	DEVIATION FROM ACCEPTABLE LIMIT OF 0.14 µg/kg/body Weight/day (mg)
PS1	0.237	0.00900	0.00760
PS2	0.009	0.00030	-0.00104
PE3	0.006	0.00020	-0.00120
PS4	0.085	0.00340	0.00200
PS5	0.079	0.00310	0.00180
PS6	0.140	0.00560	0.00420
PS7	0.016	0.00064	-0.00076
PS8	0.084	0.00336	0.00196
PS9	0.039	0.00156	0.00016
PS10	0.250	0.01000	0.00860
PS11	0.051	0.00204	0.00064
PS12	0.124	0.00496	0.00356
PS13	0.036	0.00144	0.00004
PS14	0.524	0.02096	0.01956
PS15	0.134	0.00536	0.00396
PS16	0.096	0.00384	0.00244
PS17	0.021	0.00084	-0.00056
PS18	0.038	0.00152	0.00012
PS19	0.146	0.00584	0.00444
PS20	0.050	0.00200	0.00060

Discussion

The qualitative analysis of lead is based on its ability to form precipitate when it reacts with certain compounds or reagents. Although potassium chromate is known to form yellow precipitate of lead chromate in presence of compound containing lead, it was observed that the yellow precipitate was not visible in any of the test sample. This may be due to

interference from the colorant in the formulation at very low concentration of lead or absence of lead cation. However, brown sediment was observed after centrifugation for 1 minute in 7 brands.

Lead concentration ranging from 0.006 mg/l to 0.524 mg/l was detected in all of the twenty (20) brands using atomic absorption spectrometer model AAS MODEL-SOLAAR 969 UNICAM. The quantitative determination of lead was done after digestion of the

samples. This help to eliminate organic matter, interfering ions and expose the lead in the sample.

Lead enters the body from the air during breathing, but most of it is taken in orally, where it is a component of food, beverages, drugs, supplements, and almost anything else that is ingested.

The procedure in the synthesis of paracetamol may not be responsible for lead contamination but the excipients, contaminated processing equipment used in manufacturing of the oral liquid formulations or water supply may be the source of lead contamination [16].

All the brands of paracetamol oral liquid formulation had lead concentration ranging from 0.006-0.524 mg/l. The lead concentration is less than the lead limit of 10 ppm (10 mg/kg) specified for all pharmaceutical product by in United States of America [11]. Lead is known not to be safe at any concentration in children. It is much more harmful to children than adults [5].

The centers for disease control (US) has set the standard elevated blood lead level for adults at 25 µg/dL of the whole blood. Children are at a higher risk of lead poisoning and children with blood lead level of less than 10 µg/dL can be associated with neurological injury [6].

The World Health Organization has established a tolerable weekly intake level for lead at 1.5 mg corresponding to a daily lead intake of just over 0.2 mg (200 µg), while the daily limit of less 0.14/body weight/day was specified in United State pharmacopoeia 2006. Lead consume by a year old child weighing 10 kg from all the different brands of paracetamol oral liquid formulation were less than the daily limit specified by WHO. Sixteen brands (80%) exceeded 0.14/kg weigh/day specified by USP 2006. While only four brands (20%) had lead concentration less than the daily limit specified in USP 2006.

Sample PS14, PS10, PS1, PS19 and PS6 had the highest concentration of lead. PS14, PS1 and PS6 were manufactured in the industrial areas of South

West Nigeria, specifically in Agbara Ogun State, Sakpara Ikeja, Lagos State and Ajao-Isolo Lagos respectively. These Industrial areas had been assessed for atmospheric metal deposition and the report revealed high lead contamination in these areas [12]. PS14 had a higher lead contamination which may be due to factors other than environmental contamination. The fact that it is a suspension containing a suspending agent like carboxyl methyl cellulose known to contain lead as contaminant may has contributed to the high lead concentration detected [17].

PS10 the second highest lead concentration was manufacture in Kaduna, an area where incident of lead poisoning has been previously reported [3]. PS19 was manufacture in Ogidi, Anambra State, An area known for industrial activities. Lead contamination is known to be associated with industrial activity which is attributed to geogenic and anthropogenic pollution. Low level of lead concentration was detected in products manufactured in States with less industrial activities. These states include Edo, Kwara, Niger and Abuja.

Lead gets to the body majorly by inhalation and ingestion. Oral intake of pharmaceutical product contributes to the blood lead level. Paracetamol is an over the counter drug. It is frequently and easily misused. It account for the highest incidence of drug poisoning in the United State [4]. Because of the accumulative effect of lead, the reduction and prevention of lead in paracetamol oral formulation is vital in controlling the blood lead level in children who are among the group susceptible to lead poisoning. Evidence that children chronically exposed to high lead concentrations suffer neurological defect has forced developed countries to reduce lead pollution and lead content of manufactured items [18]. Blood lead concentrations in United Kingdom have fallen substantially since 1984 [19].

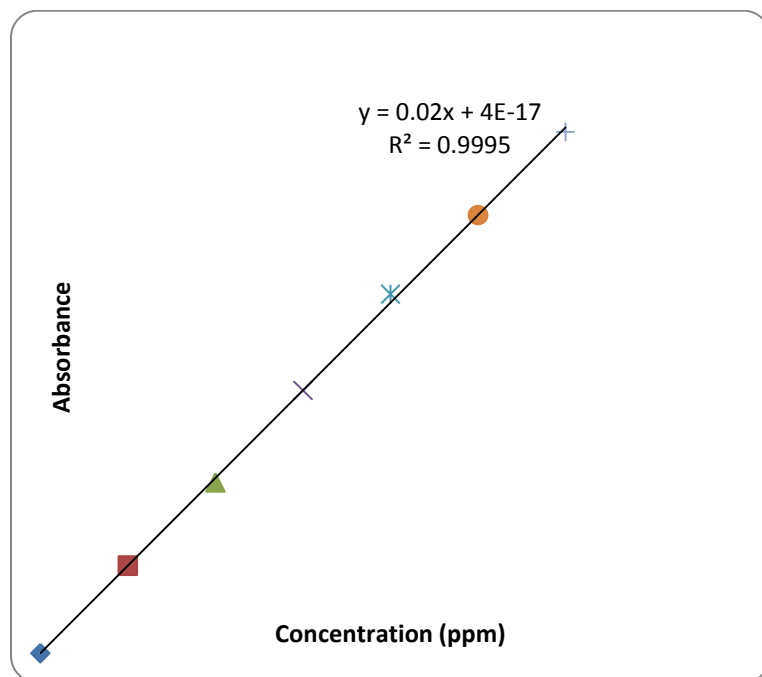


Figure 1: Calibration Curve for Lead

TABLE 3: RESULT FOR ANALYSIS OF LEAD IN DIFFERENT BRANDS OF PARACETAMOL ORAL FORMULATION

VARIABLES	PROPORTION (%)
QUALITATIVE ANALYSIS	7 (35%)
Number of brands where Lead was detected	
QUANTITATIVE ANALYSIS	20 (100%)
Number of brands where Lead was measured	
Distribution of lead concentration (mg/L)	
0.000	Nil
0.000-0.001	Nil
0.001-0.010	2 (10%)
0.010 – 0. 100	11 (55%)
0.100 – 0. 200	4 (20%)
0. 200 – 0. 500	2 (10%)
> 0. 500	1 (5%)
Estimated daily intake from 40 ml (mg/day)	
< 0. 0014	4 (20%)
0.0014 – 0. 020	15 (75%)
0. 020 – 0. 100	1 (5%)
> 0. 200	Nil

APPENDIX: MONOGRAPH OF SAMPLES USED IN THE STUDY

CODE	BRAND NAME OF DRUG	MANU. DATE	EXP. DATE	NAME AND ADDRESS OF MANUFACTURER	NAFDAC NUMBER	BATCH
PS1	Maxipol Paracetamol Suspension	0513	0516	SKG-Pharm Ltd 7/9 Sapara Street, Ikeja, Lagos For Auro Pharma Ltd 11, Kaara street, Off Isolo way Ajao Estate, Lagos	A4-5668	C31301
PS2	Lotemp	1113	1016	Unique Pharm. Ltd km 38 Abeokuta Road, Sango-Ota Ogun State	04-4988	L053080
PE3	Paracetamol	0913	0816	Nomagbon Pharm. Ltd 43 Oyemwen Street New Benin, Benin City, Edo State	04-2431	E11548
PS4	M& B Paracetamol	0214	0117	May & Baker Nigeria 1 May & Baker Avenue Off Idiroko Road Ota, Ogun State	04-0247	A140058
PS5	Paracetamol syrup	1212	1215	Peace Standard Pharm. Ind. Limited Plot 3 & 5 Adewole Industrial Estate Lubcom Avenue Ilorin, Kwara State	04-4836	556
PS6	Emzor Paracetamol syrp	0214	0217	Emzor Pharm. Ind. Ltd 10 Kolawole Slwnbare street Ajao Estate Isolo-Lagos	04-0289	L1971
PS7	Panda Paracetamol Syrup	0813	0816	Afrab-Chem Ltd 22 Abimbola Street, Isolo Ind. Estate Isolo-Lagos	04-1918	13252
PS8	Mildol	0.314	0217	Asad Pharm. Ltd Plot 50 Independent road, Kawaji, Kano	04-5579	BN6212
PS9	Palmol Paracetamol	0314	0317	Pal Pharm. Ind. Ltd Plot 102 Maganda road, Bmpai Ind. Area, Kano	07-1427	3156
PS10	Mecmol Paracetamol	0214	2016	Abumec Pharm. Ltd No. 7 Ligari Road Sabon Tasha Kaduna	04-1799	ED2404
PS11	Labcetamol syrp	0314	0217	Ugolab Productions 157/159 CLUB ROAD Bompai Ind. Lagos Kano	04-1960	354APA
PS12	Age-Mol Paracetamol syrup	1013	0916	Newage Pharm. Ind. Ltd Plott 231/234 Kuje Road Gwagwalade Abuja	04-9833	AM-13-010
PS13	Paradana Paracetamol syrup	1113	1016	Dana Pharm. Ltd Shiroro Dam Road Maitumbi Minna Niger State.	04-8286	PL3096
PS14	Calpol Paracetamol suspension	1212	1115	Evans Medical Plc. Km 32 Lagos-Badagry Expressway, Agbara Indsutrial Estates, ogun State for Glakosmithkline pharm. Nig. Ltd. Industrial Avenue, Ilupeju Lagos	04-1892	2MOOIV
PS15	Aripol Paracetamol suspension	1213	1116	Fidson Health care Plc, Km 38 Lagos Abeokuta Express-way Sango-Ota Ogun State	04-4744	LA818013
PS16	Esimol Pracetamol	0414	0317	Esehi Pharm. Ind. Ltd 48 2nd Isuwa Lane, Off M. M. Way Benin City, Edo State	04-7836	BNM0507
PS17	Architamol	0613	0615	Archy pharm. Nig. Ltd 30 win Funke Street by Access Bank Junction Off Ahmadiya B/Sttop Lagos Abeokuta Express Way Ojokoro Lagos	04-5621	PS1303
PS 18	Drugamol Paracetamol syrup	0214	0117	Drugfield pharm Ltd. Lynsonchemical Avenue, km 38 Lagos-Abeokuta Expressways, Sanjo Ota Ogun State	04-8333	14760201
PS19	KP Paracetamol syrup	1112	1015	King Size Pharm Nig. Ltd KM 15 Old Enugu Road, Ogidi, Anambra State.	04-1859	SM3376P
PS20	Barbimol Children's Paracetamol syrmp	1213	116	Junel Nigeria Ltd 35, Nwkubor Road Erhene-Enugu Enugu State	04-6401	BN+0069

CONCLUSION

Paracetamol is an important medication needed in a basic health system [20]. Twenty brand of paracetamol oral liquid formulation had an average lead concentration of 0.108 mg/l. This will produce an estimated maximum daily dosage of paracetamol oral liquid formulation that contains 0.00432mg of lead in a year old child weighing 10 kg. This amount of lead consume in a day exceeds the daily lead limit recommended by USP 2006.

Findings obtained from present research demands that there should be standard lead limit for manufactured items most especially food and pharmaceutical products consumed by children which are more vulnerable to lead poisoning both at acute and chronic level of exposure.

DISCLOSURE STATEMENT

The authors have no conflict of interest to declare

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