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Original Article

Heavy Metals in Over-the-Counter Pediatric Drugs Locally Produced in Uganda: A Stare at Manganese, Lead, and Cadmium

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Abstract

This study evaluated the amounts of lead (Pb), cadmium (Cd), and manganese (Mn) in pediatric over-the-counter medications made in Uganda. Twelve distinct brands from four categories of pediatric medications (antihistamine, cough expectorant, antipyretic and analgesic, and cold and flu medication) were chosen at random from Kampala's drug stores. Before acid digestion, the syrups were washed with concentrated HNO_3:$HClO_4$ (5:1), and the metals were measured using FAAS AAnalyst 400. The average values (µg/mL) found were as follows: antihistamine (Cd, 0.89±0.122; Pb, 7.01±10.0); cold and flu (Cd, 0.89±0.073; Pb, 1.69±0.718); cough expectorant (Cd, 0.14±0.0196; Pb, 1.55±1.332); and antipyretics and analgesic (Cd, 0.16±0.774; Pb, 1.76±1.123). Antihistamines and medications for the cold and flu were not detectable in sample codes (A1 and B1), respectively. In every sample examined, manganese levels were below the non-detectable threshold. The different coefficient of variation (CV) values found in this investigation demonstrated that the metals in pediatric medications came from a wide variety of sources. According to total metal content, each brand of pediatric medication contains Antihistamine (56%), Antipyretic and analgesic (15%), Cold and flu (15%), and Cough expectorant (14%). Uganda's pediatric medicine producers should be closely watched by the National Drug Agency.

Keywords: Public health, Medicine, Contamination, Toxicology, Self-medication.

1. Introduction

Health experts have expressed worry over the presence of trace elements in pediatric over-the-counter (OTC) medications designed for infants and toddlers. It has been a serious concern that the stunted growth common in the majority of low- and middle-income countries of the world is caused by neurobehavioral problems in infants and toddlers that can be linked to heavy metal contamination in OTC pediatric medications given to infants and toddlers. It has been demonstrated that heavy metals interact quite strongly with human biological systems. Numerous ligands,

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particularly proteins with sulfhydryl groups, are present in human body cells and can bind with both essential and non-essential metals, hiding more than 200 enzymes in the body [1]. It is concerning that lead (Pb) has negative effects on the growth and development of newborns and toddlers in low- and middle-income countries [2, 3]. It has been discovered that high Pb concentrations in children's blood are inversely connected to low intellectual quotient (IQ) and a decline in reasoning abilities up to the first seven years of age [4]. The central nervous system is the primary target organ for Pb toxicity in humans.

More than fifty countries throughout the world have drinking water with more than 400 µg/L of manganese (Mn), according to studies [5].

OTC like antipyretic, cough syrup, cold, and flu medications are frequently used for self-medication since they are readily available at drugstore counters with or without a doctor's prescription. Parental self-medication in infants and toddlers without consulting a doctor or getting a prescription at the hospital is becoming more and more common. More than half of medicines consumed globally, according to WHO [6], are taken without a prescription. According to Ocan et al. [7], three-quarters of adult residents of Northern Uganda admit to using antimicrobial medications without a prescription. Ninety-nine percent of children under the age of six were found to have received parental self-medication, with 39 percent having previously used drugs. According to Orisakwe et al. [8] ninety-nine percent of children under the age of six were found to have had parental self-medication, with 39 percent having used medications twice before receiving a prescription or guidance from a doctor in a hospital. In Uganda, Ocan et al.'s report [9] detailed the prevalence of administering children non-prescription medications, including antimicrobials (44.8%), cough medicine (83.1%), unspecified fever (69.7%), and flu treatments (84.9%).

The children population of Uganda is divided into two age groups: 0–8 years (30.9%) and 6–12 years (21.3%) [9]. According to the Uganda Bureau of Statistics (2014) [10], fifty-five (55%) percent of Uganda's population is considered a child because they are under the country's constitutional legal age of 18, and this age group has the highest death rate related to the indiscriminate use of non-prescription pediatric drugs. Other potential health risks, in addition to the indiscriminate use of non-prescription pediatric medications, include drug resistance and drug-to-drug interactions, which have been linked to a death rate of 2.9–3.7% worldwide [11]. In particular, for infants and toddlers who self-medicate, the presence of heavy metals in OTC pediatric medications might exacerbate the public health consequences.

There are few studies on newborns being exposed to metals in Uganda [12, 13], and there is no comprehensive literature on trace elements in over-the-counter pediatric medications and their effects on infants and toddlers in Uganda. This study evaluated the levels of manganese, lead, and cadmium (Cd) in four distinct brands of OTC pediatric pharmaceuticals that are frequently produced in Uganda to identify the likely sources of heavy metals in OTC pediatric drugs in that country.

The research's conclusions have some political repercussions. The findings of this study express the source of pollution and its effects on the health of babies and young children. The probable amounts of metal contamination and associated potential health consequences will also be known to the local communities. By avoiding, limiting, or using mitigation actions in response to the potential metal contamination of OTC pediatric medications, the affected and interested parties will benefit from the information-sharing in this study.

2. Materials and Methods

2.1. Sample Categories

In this study, twelve different brands of over-the-counter medications manufactured locally in Uganda and frequently used to treat various illnesses in children were used. These brands were divided into four categories: cold and flu, cough expectorant, antipyretics and analgesic, and antihistamine. Three brands from various manufacturers in each category were acquired from various Kampala pharmacy stores. For replication analysis, two batches of each of these brands were bought.

2.2. Acid Digestion, Analysis, and Quality Control

All glassware and sample bottles were meticulously cleaned with liquid soap, rinsed with distilled water, submerged in 10% nitric acid for 48 hours, rinsed with water, and then rinsed again with water and distilled water. A 105 °C oven was used to dry the glassware. Nitric and perchloric acids had analytical grades and came from FINAR Ltd. from India. To reduce contamination, the water used was distilled three times. Using nitric acid (5 mL) and perchloric acid (1 mL) in a beaker placed on a thermostatically controlled hot plate for a duration of around 45 minutes, 25 mL of syrup samples and 1.0 g of solid samples were acids digested until the sample volume remained around 2 mL. To prevent complete drying out and fire explosions that could happen as a result of the perchloric acid, the mixture was periodically supplied with nitric acid. The syrups were ashed before being consumed. Each digested combination was filtered, chilled, and made up to mark in a 50 mL standard flask with distilled water. Before measurement using a flame atomic absorption spectrophotometer (FAAS), the digested samples were stored in a refrigerator. The digested samples were examined using an autosampler-equipped AAnalyst 400 flame atomic absorption spectrometer from the Uganda Industrial Research Institute (UIRI).

All of the samples were subjected to a blank analysis. In the absence of the drug samples, an identical volume of each reagent employed in sample digestion was measured and processed. Next, one of the digested samples was subtracted from the value obtained for each metal. Drug recovery analysis was carried out by splitting the drug sample into two equal sections, one of which was spiked with a known concentration of the target analyte while the other was left unspiked. The two samples were digested using the previously described above technique. The recovery percentage for each metal was then determined. The levels used to plot the calibration plots for the Cd and Mn were 0.00, 0.5, 1.0, 1.5, 2.0, and 2.5 µgmL-

[1]. Lead was measured using a five-point calibration scale with values of 0.00, 10.0, 20.0, 30.0, and 40.0 µgmL-[1]. A stock solution of 1000 mg/L was prepared using common reference materials.

2.3. Analytical Statistics

The raw data were processed using an Excel file, and IBM SPSS software version 20 was used for the descriptive analysis. For the heavy metals in OCT medicines, descriptive analysis (mean, standard deviation, and coefficient of variation) was established.

3. Results and Discussion

3.1. Appraisal of Analytical Protocols Employed

Regarding percentage recovery (% recovery), the limit of detection (LOD), the limit of quantification (LOQ), and linearity of calibration (r^2), the validity of the analytical technique used in this study was evaluated. Mn, Cd, and Pb had a linear calibration of 0.975448, 0.989258, and 0.987033 respectively. Mn, Cd, and Pb have LOD and LOQ of 0.02 mg/L, 0.01 mg/L, and 0.02 mg/L, respectively. The highest rates of recovery (%) for metals were for Cd (92.6), Pb (91.8), and Mn (90.5) (**Table 1**).

Table 1: Calibration Parameters, % Recovery, LOD & LOQ of Metals.

	Cd	Mn	Pb
γ (nm)	228.80	279.50	283.31
Cal. Curve (r^2)	0.989	0.975	0.987
%R	92.6	90.5	91.8
LOD (µg/mL)	0.01	0.02	0.02
LOQ (µg/mL)	0.1	0.2	0.2

Table 2 lists the metal concentrations (µg/mL) in pediatric antihistamine medications. In sample A1, cadmium levels were below the limits of detection. Cd had a mean value of 0.89±0.012 with a range of not detected (Nd) in (A1) and 0.25 µg/mL (A3). Mn was below the pediatric antihistamine medication's detection limit. Pb had a mean value of 7.01±10.0 and ranged from 0.32±0.052 in A1 to 20.35± 0.117 in A3. The coefficient of variation (CV) ranged from 0.00 in Mn to 142 in Pb. The variable amounts of metals in the anti-histamine pharmaceuticals studied could be explained by the fact that the metals in pediatric anti-histamine medications came from a variety of diverse sources.

Table 2: Cd, Mn, and Pb levels of metals (µg/mL) of anti-histamine drugs.

Paediatric Drugs	Cd	Mn	Pb
A1	<0.01	<0.02	0.32 ± 0.052
A2	0.02 ± 0.007	<0.02	0.37 ± 0.032
A3	0.25 ± 0.004	<0.02	20.35 ± 0.117
Mean ±SD	0.89 ±0.122	0.0	7.01 ± 10.0

Table 3 displays the results of the metal concentrations (µg/mL) in the B1-B3-coded cold and flu antiviral medications. Cd varied from Nd in B1 to 0.17± 0.002 in B3, with a mean value of 0.89± 0.073, and was below the detection limit in B1. In B1–B3, Mn was below the non-detectable limit. Pb levels varied between 0.84 ± 0.026 in B2 and 2.84± 0.127 in B3, with a mean value of 1.69

Table 3: Cd, Mn and Pb levels (µg/mL) of Cold and Flu Drugs.

Paediatric Drugs	Cd	Mn	Pb
B1	<0.01	<0.02	1.74 ± 0.114
B2	0.10± 0.001	<0.02	0.84 ± 0.026
B3	0.17 ± 0.002	<0.02	2.84 ± 0.127
Mean ± SD	0.89 ± 0.073	0	1.69 ± 0.718
CV	8.2	0	42.5

±0.718. The coefficient of variation's findings, the values varied from 0.00 to 42.5. Comparing the variation to other OTC medicine categories taken into account in this study, it was not excessively wide.

Table 4 displays the metal concentrations (µg/mL) in cough expectorant OCTs medications. Pb levels varied between 0.58 ± 0.136 in C1 and 3.32 ± 0.40 in C3, whereas Cd levels ranged from 0.07± 0.013 in C2 to 0.27 ± 0.003 in C3. The mean values for Cd and Pb were 0.14± 0.09 and 1.55 ±1.332, respectively. All of the OTC cough-expectorant medications had manganese levels that were below detection. The CV was 0.00 for Mn and 73.1 for Pb.

Table 4: Cd, Mn and Pb levels (µg/mL) of Cough Expectorant Drugs.

Pediatric Drugs	Cd	Mn	Pb
C1	0.08 ±0.009	<0.02	0.58 ± 0.136
C2	0.07 ± 0.013	<0.02	0.76 ± 0.034
C3	0.27 ± 0.003	<0.02	3.32 ± 0.040
Mean ± SD	0.14 ± 0.096	0	1.55 ± 1.332
CV	68.6	0	73.1

Table 5 lists the metal concentration (µg/mL) in antipyretic and analgesic OTC medications. The levels of Pb were 0.79± 0.102 in D1 and 3.23 ±0.087 in D3, whereas the levels of detectable Cd ranged from 0.08± 0.003 in D1 to 0.26± 0.003 in D3. For Cd and Pb, the mean values (µg/mL) are 0.16± 0.774 and 1.76± 1.123, respectively. Mn levels in every sample were below the threshold for detection. Between 0.00 in Mn and 483.8 in Cd, the CV values fell.

Table 5: Cd, Mn, and Pb levels of metals (µg/mL) of Antipyretics and Analgesics Drugs.

Pediatric Drugs	Cd	Mn	Pb
D1	0.08 ± 0.003	<0.02	0.79 ± 0.102
D2	0.14 ± 0.001	<0.02	1.27 ± 0.077
D3	0.26 ± 0.003	<0.02	3.23 ± 0.087
Mean ± SD	0.16 ± 0.774	0	1.76 ± 1.123
CV	483.8	0	63.8

According to **figure 1**, the following brands of pediatric medications contain the most metal overall: Antihistamine (56%) > Antipyretic and analgesic (15%) = Cold and flu (15%) > Cough expectorant (14%). The magnitude of the metal load in antihistamines was four times more than that in the other three pediatric medication groups.

Pediatric age groups (infants and toddlers) are particularly susceptible to hazardous metals due to their high intestine absorption capacities, ineffective excretion, excessive food consumption, and body weight ratio [15]. This study's main objective was to evaluate the quantities of heavy metals (Pb, Cd, and Mn) in OTC pediatric medications made in Uganda. There has not been any prior research on this topic in Uganda, according to the literature. The analytical procedure used in this study's analysis proved the correctness and dependability of the metal concentrations in the samples used in this investigation. The study's percentage recovery fell within the European Union guideline's range of 70 to 100% for evaluating the analytical method's accuracy and precision. The resulting calibration plots obtained had very excellent linearity and were consistently judged to provide accurate metal concentrations in the medication samples.

According to the study's findings, Pb was present in every single sample and Cd in 83% of the sample size while Mn was not detected in all the samples. The OTC antihistamine with the highest Pb level was 7.01µg/mL, and the cough expectorant with the lowest level was 1.55 µg/mL. This value was higher than the Pb

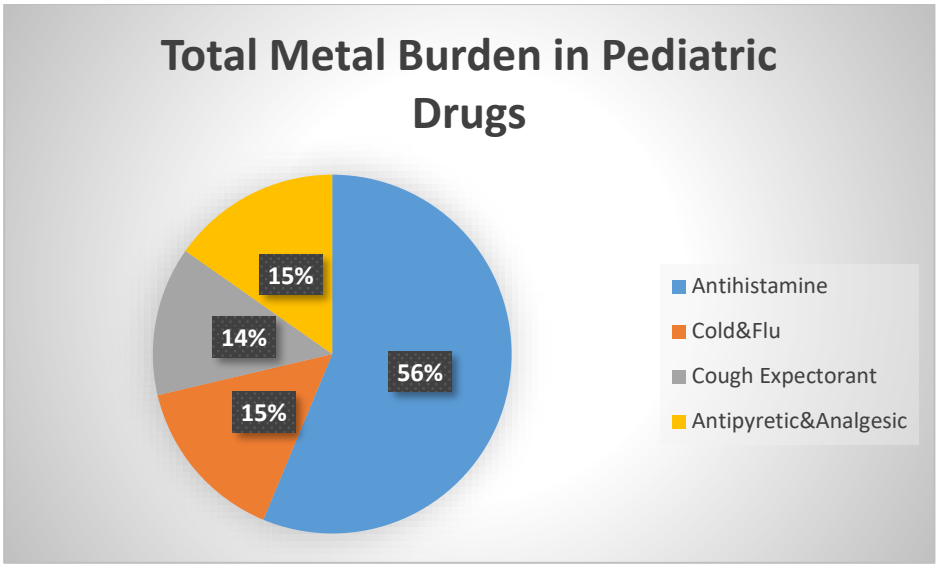

Figure 1. Total Metal Burden in Pediatrics Drugs.

concentrations found in locally made pediatric syrups for children in Nigeria, which ranged from 0.01 mg/L in cadiphen produced in Dholka, India, to 0.09 mg/L in maxiquine produced in England [16]. When compared to a similar report of Pb levels (Nd -6.75 µg/mL) in pediatric drug manufacture in Nigeria reported by Oyekunle et al [17] but lower to Nd -0.7 mg/L in analgesic syrups reported by Nnaneme [18], there was no statistically significant difference between the levels of Pb in locally manufactured pediatric drugs obtained in this study. The levels of Pb found in this investigation were higher than the EFSA-set threshold limit [4]. Pb is absorbed more readily in youngsters than in adults, where it is then stored in tissue before being incorporated into bone (EFSA, 2010[4]). Early Pb exposure has been associated with several negative health effects, including postnatal growth inhibition, behavioral issues, impaired cognition, and delayed puberty [1].

Cd was the highest level in antihistamine, cold, and flu (0.89 mg/L), while in cough and expectorant, the level was the lowest (0.14 mg/L). The amount of Cd found in this study was found to be lower than that found in locally produced pediatric syrups in Nigeria, which ranged from 0.01 mg/L in emzolyn and colipan to 2.45 mg/L in magcid suspension. However, it was comparable to that found in 0.01 mg/L of Bellis cough syrup made in Southport, England, and 0.88 mg/L in Zentel albendazole syrups made in Bangalore, India [16]. In pediatric over-the-counter medications described by Oyekunle et al [17] and in analgesic syrup reported by Nnaneme [18], 1.1-3.5 mg/L Cd was below the non-detectable level. High blood pressure, myocardial dysfunction, and other bone abnormalities are all equally correlated with Cd [19]. Children may also exhibit symptoms of vomiting, nausea, obstructive lung and renal dysfunctions, muscle weakness, and abdominal cramps depending on the extent of exposure [20].

In this investigation, manganese levels in all four sets of pediatric OTC medications made in Uganda were 100% non-detectable. Nduka and Orisakwe [21] reported pediatric medications produced locally in Nigeria (28.38 and 4.37 mg/L in Ferobin and Jawaron syrups), as well as ranging values (0.02 mg/L in Dholka, India, and Southport, England), and (0.36 mg/L in Mumbai, India. In Nigerian-made OTC pediatric

medications, Mn range values of 0.04 to 2.39 mg/L were reported by Oyekunle et al. [17]. The recommended daily limit of Mn is 3 µg for infants between the ages of 0 and 6 months, and 1600–1900 µg for children between the ages of 9 and 13 years [22]. Mn helps children's skeletons develop to their maximum potential, promotes rapid wound healing, increases collagen production, and activates proline and prolidase, enzymes that help produce collagen and amino acids, respectively [23]. However, studies have shown that kids who drank water with high levels of Mn were found to have neurobehavioral disorders like short- or long-term memory loss, visual impairment, and verbal indices deficits [24–26]. Pediatric oral liquid medications produced in Bangladesh had a 20% measurable level of Mn but no detectable levels of Pb or Cd, according to Hossain et al. [14]. The use of contaminated water, poor hygiene and storage facilities, and inadequate testing of raw materials, packing, and processing, such as lead solder, may be blamed for the potential entry points of these metals into the medications [16]. According to Nnaneme [18], the sources of Cd and Mn in medications could also include food, contaminated water, and industrial effluents.

Assuming that these medications are given to children in doses of 10 mL three times per day, the amount of Pb and Cd they may consume would be significantly higher than the permissible daily exposure (PDE) recommended by the United States Pharmacopoeia (USP), International Conference on Harmonization (ICH), and European Medicine Agency (EMEA) (**Table 6**). Ugandan children's health would be seriously hampered by the use of pediatric medications made in this country.

Table 6: Calibration Parameters, % Recovery, LOD&LOQ of Metals.

	Cd	**Mn**	**Pb**
USP oral PDE (µg/day)	10.25	NE	2.05
ICH oral PDE (µg/day)	2.05	NE	2.05
EMA oral PDE (µg/day)	NE	NE	NE

4. Conclusion

Three inorganic pollutants (Pb, Cd, and Mn) were examined in this study in four different types of over-the-counter pediatric medications made in Uganda. The assessment of heavy metals in pediatric over-the-counter medications has not before been done in Uganda. The four kinds of OTC pediatric medications that were taken into consideration were all found to contain Pb and Cd, according to this study. In all four pediatric medication brands, manganese levels were below non-detectable limits. Health officials are concerned about the presence of non-essential elements (Pb and Cd) and their excessive amounts in these pediatric medications made in Uganda. Other essential and non-essential metals in OTC pediatric medications, infant foods, and frequently consumed beverages by kids could be the subject of further research. The National Drug Agency should continuously watch over how these medications are made.

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None.

Conflict of interest

The authors declare to have no conflict of interest.

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