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QUALITY CONTROL OF SOME PEDIATRIC ORAL PREPARATIONS IN NIGERIAN MARKET

Abu-Saeed Kamaldeen[1†], Jamiu Olakunle Muslim[1] and Abu-Saeed Muhammad Buhari[2]

ABSTRACT

The issue of faking, profiteering, adulteration, production of substandard drugs and inappropriate methods used in manufacturing of drugs is a common occurrence. These may lead to sub or non-therapeutic effect of drugs especially in children which may increase morbidity and mortality among them. Therefore, drugs need routine quality control involving both chemical and microbiological analysis be carried out on them to ensure and ascertain that they meet up to official standard in order to promote quality and efficacy. This work is thus aimed at the carrying out chemical and microbiological analysis on eleven (11) brands of paracetamol syrup, eleven (11) brands of Ascorbic acid syrup and ten (10) brands of Metonidazole suspension found in the Nigerian environment to determine their quality using official methods. Microbiological analysis was done using pour plate method and chemical analysis of percentage content of active ingredients was done using official methods according to British Pharmcopoeia. Results showed that the microbiological analysis of all the three types of oral liquid preparations gave satisfactory results. Only one brand of Ascorbic acid syrup failed the microbiological analysis based on official standards. The Chemical analysis of the products however, can generally be said to be unsatisfactory. Six out of the eleven brands of Paracetamol syrup; ten out of the eleven brands of Ascorbic acid syrup and three out of the ten brands of Metronidazole suspension all failed the chemical analysis. Most of them recorded low percentage content of their active components in the various formulations.

KEYWORDS: Pediatric Oral Preparations, Quality control, Nigerian market.

INTRODUCTION

Oral liquid preparations are among the commonest dosage forms used in compounding drugs. They usually come in solution, suspensions or emulsions containing one or more active ingredients in a suitable vehicle. Oral solutions contain one or more active ingredients dissolved in a suitable solvent, oral suspension contains one or more active ingredients suspended in a suitable vehicle while oral emulsions contain one or more active ingredients which are stabilized oil-in-water dispersions, either or both phases of which may contain dissolved solids (BP, 1998). These forms of formulation enhance the bioavailability of drug and generally produced for those who cannot swallow other forms of formulations like tablets and capsules like children and elderly (Easton, 1984).

Studies have shown that active components in oral liquid formulations are susceptible to degradation than in the solid form. This may come in form of physical or/ and chemical instability. Physical instability of liquid formulation involves the formulation of precipitates, less-soluble polymorphs, adsorption of drug substances onto container surfaces, microbial growth and changes in product appearance. Other may include colour, odour and taste (Shami et al, 1972). On the other hand, chemical instability may arise from hydrolysis, oxidation and reduction reactions (Connors et al, 1986). The extent of these reactions in a product may depend on factors like temperature and pH. Degradation of drugs generally leads to decrease availability of active ingredients in the formulation which in turn affects the efficacy of such drugs. In the case of antibiotic formulation for example, decrease active component of the drug may result in resistance. Therefore, the method of formulation of liquid oral preparation is very vital to eliminate the issue of instability and to maintain the active constituent of the drugs throughout its shelf life.

Most pediatric preparations come in oral liquid formulations. Children may react more easily to instability of a drug than an adult. For example, the immune system of a child may not be able to cope with an unstable drug which has been heavily contaminated with harmful microbes beyond recommended specification when compared to the adult. This is because the adult immune system is much more developed and capable most times of handling such situation. Reports have indicated increasing number of infections caused by contaminated non-sterile preparation (Ibezim et al, 2002). Also, the fragile nature of children demands that appropriate dosage of drugs be administered to them when required to promptly reduce morbidity which in turns reduces mortality among them. The numerous points enumerated above require routine quality control involving both chemical and microbiological analysis be carried out on drugs to ensure and ascertain that they meet up to official standard in order to promote quality and efficacy.

[1]Research Unit, Peace Standard Pharmaceuticals, Ilorin. Nigeria.
[2]Microbiology Department, University of Ilorin Teaching Hospital, Ilorin. Nigeria.
†Corresponding author: kamal.abusaeed@yahoo.com

In addition, the issue of faking, profiteering and adulteration of drugs is also a common occurrence in our economy. Counterfeiting of pharmaceutical is a global problem (Akunyili, 2004). These flood the market with fake or substandard drugs which are ineffective against their intended purpose. All these bottlenecks lumped together also contribute to the need for strict routine quality control of all drugs in our environment. In Nigeria, Paracetamol, Ascorbic acid and Metronidazole are among the drugs commonly found and used in pediatrics. These drugs have been formulated into oral liquid formulations.

Paracetamol also known as acetaminophen is one of the most common 'over-the-counter' drug used in children because its safety and efficacy are well established (Lesko et al, 1999). It is an analgesic and an anti-pyretic drug. It is generally not classified as a Non-Steroidal Antinflammatory Drug because of its weak antinflammatory property. It is also a major ingredient in numerous cold and flu remedies. While generally safe for use at recommended doses, acute overdoses of paracetamol can cause potentially fatal liver damage and in rare individuals, a normal dose can do the same (Larson et al, 2005). Reviews have identified inappropriate dosing as one of the reasons for hepatotoxicity by acetaminophen in children (Rivera-Penera et al, 1997; Heubi et al, 1998). Therefore, correct dose in formulations are very essential to avoid this. Pediatric preparations come in solutions and suspensions.

Ascorbic acid also known as Vitamin C is a white solid, naturally occurring and a form of vitamin. Many animals are able to produce it but humans require it as part of their nutrition (Lachapelle and Drouin, 2010). Ascorbic acid is found in plants, animals and single cell organisms where it is produced from glucose (Stone 1972). Deficiency of Vitamin C results in scurvy and thus used in the treatment of the disease (Ana-Maria and Magearu, 2004). Other uses include treatment of common cold, infections including gum disease and glaucoma among other uses (Carr et al, 1981). Ascorbic acid has been known to degrade easily especially upon exposure to air. This is because it is a mild antioxidant and undergoes oxidation easily. Therefore, extreme care has to be taken when manufacturing dosage forms of this drug so as not to lose the active component to oxidation, a form of chemical instability (Lachapelle and Drouin, 2010). It is not unlikely to find poorly formulated Vitamin C solution which does not reflect the label claim as regards the quantity of the Ascorbic acid in the formulation.

Metronidazole is an amebicidal, antibiotic and antiprotozoal drug which acts by disrupting DNA and nucleic acid synthesis in the organism (Kucers et al, 1997). It has a wide range of clinical use among which is that it is used in treatment of serious infections caused by susceptible anaerobic bacteria, such as B. fragilis, Clostridium, Fusobacterium, Peptococcus and Peptostreptococcus species (Cohen et al, 2010). More importantly, it has been used orally in the treatment of antibiotic induced diarrhea and colitis which is a very common occurrence in children. All antibiotics, including metronidazole has to be formulated in order to contain and

deliver the exact quantity of active ingredient required because sub-standard doses may result in resistance of the microorganism to the drugs. Pediatric metronidazole comes in form of suspension.
This work is thus aimed at the carrying out chemical and microbiological analysis on eleven (11) brands of Paracetamol syrup, eleven (11) brands of Ascorbic acid syrup and ten (10) brands of Metonidazole suspension found in the Nigerian environment to determine their quality using official methods.

MATERIAL AND METHODS

Samples

All the available commercial brands of Paracetamol syrup, Ascorbic acid syrup and Metronidazole suspension in the various local pharmacy shops in Kwara state, Nigeria were used for this study. This amounted to the use of eleven (11) brands of Paracetamol syrup, eleven (11) brands of Ascorbic acid syrup and ten (10) brands of Metronidazole suspension. All samples were not expired as at the time of this study according to the expiry date indicated on the labels and secondary packaging materials of the samples.

Microbiological analysis

Microbiological analysis was carried out using the pour plate method.The procedure for bacteria count involved pipetting 10ml of the sample into 90ml of Nutrient broth and mixed properly. Then, 1ml of the resulting mixture was pipetted into sterile plates in duplicate and 20mls of prepared sterile Nutrient Agar (NA) was also poured into each plate and cooled to 45^{0}C. The plates were swirled for even distribution and allowed to solidify. The plates were incubated at 37^{o}C for 48hours. Bacteria count was estimated using a colony counter and then multiplied by the dilution factor to obtain the total count. The procedure for fungi count include pipetting 1ml of the sample in Nutrient broth (as described above under bacteria count) into four sterile plates and then 20ml of sterile Sabourand Dextrose Agar (SDA) was poured into each plate and swirled to allow for even distribution. The plates were incubated at 25^{o}C for five days. The fungal count was estimated using a colony counter and then multiplied by the dilution factor to obtain the total count.

Chemical analysis

Official methods were used for the chemical analysis of individual samples as follows:

1. Paracetamol syrup

5ml of the syrup was added to 50ml of 0.1M sodium hydroxide and diluted to 100ml with distilled water in a 100ml standard flask. The mixture was shaken and diluted to 200ml in a 200ml standard flask. 10ml of the above solution was diluted with distilled water to 100ml in a standard flask. Finally to 10ml of the resulting solution was added 10ml of 0.1M sodium hydroxide and diluted to 100ml with distilled water in a standard flask.The procedure was also repeated for Paracetamol standard with the weights 0.118g, 0.119g-0.122g for syrup containing 120mg/5ml and 0.123g, 0.124g-0.127g for syrup containing 125mg/5ml.The absorbance's of the prepared samples (syrup and standard) were measured in a UV spectrophotometer at a wavelength of 257nm using a mixture of 10ml of 0.1M sodium hydroxide and 90ml of distilled water as blank (BP, 2007).

2. Ascorbic acid syrup

5mls of syrup was pipetted into a 250ml conical flask. Then 5mls of 2M Sulphuric acid was added to this. This was then followed by the addition of 20mls of distilled water and mixed. The resulting solution was titrated with 0.05M of Iodine solution using starch mucilage as indicator. Each ml of 0.05M Iodine is equivalent to 0.008806g of Ascorbic acid (BP 1998).

3. Metronidazole suspension

Standard solution was prepared by taking 50mg of standard powder in 100mls of 0.1N Hydrochloric acid. This was shaken for 15minutes and then sufficient 0.1N Hydrochloric acid was added to produce 200mls.The resulting solution was filtered and 5mls of the filtrate diluted to 100mls with 0.1N Hydrochloric acid. The sample suspension was prepared the same way by taking equivalent of 50mg of Metronidazole in the suspension. The absorbance of both standard and samples were read at 277nm taking 375 as the value of A (1%, 1cm). (BP 1998)

RESULTS

All the Paracetamol syrup samples were coded P1 to P11; all the ascorbic acid syrup samples were coded A1 to A11 while all the Metronidazole suspension samples were coded M1 to M10. The results obtained from the Microbiological and Chemical analysis are as presented in the tables below.

Table 1. Results obtained from the Chemical and Microbiological analysis of various samples of Paracetamol syrup

Sample code	Batch No	Claimed strength (mg per 5ml)	Chemical analysis	Microbiological analysis		
			% content of Paracetamol	Bacteria count (cfu/ml)*	Fungi count (cfu/ml)*	Pathogen (cfu/ml)*
P1	0511	120	90.05	Nil	Nil	Nil
P2	IJ450002	125	100.94	Nil	Nil	Nil
P3	LOTMA1788	120	84.38	Nil	Nil	Nil
P4	L10210	125	96.20	Nil	Nil	Nil
P5	PP518	125	103.79	10	Nil	Nil
P6	APC020	125	101.28	Nil	Nil	Nil
P7	LS15X	125	94.28	10	10	Nil
P8	1107S	125	82.85	Nil	Nil	Nil
P9	LOS0042	125	100.00	Nil	Nil	Nil
P10	BPL0114	125	102.85	10	10	Nil
P11	TPS58	125	86.22	Nil	Nil	Nil

*cfu/ml= colony forming unit per milliliter

Table 2. Results obtained from the Chemical and Microbiological analysis of various samples of Ascorbic acid syrup

Sample code	Batch No	Claimed strength (mg per 5ml)	Chemical analysis	Microbiological analysis		
			% content of Ascorbic Acid	Bacteria count (cfu/ml)*	Fungi count (cfu/ml)*	Pathogen (cfu/ml)*
A1	VC13	100	86.05	Nil	Nil	Nil
A2	267	100	91.91	20	Nil	10
A3	CS02	100	71.18	Nil	Nil	Nil
A4	BPL0405	100	63.07	Nil	10	Nil
A5	TVCS141	100	78.39	Nil	Nil	Nil
A6	L434P	100	95.06	10	Nil	Nil
A7	006	100	90.56	20	Nil	Nil
A8	T006X	100	113.19	100	Nil	Nil
A9	KL0264	100	82.00	150	Nil	Nil
A10	PVC465	100	99.12	30	Nil	Nil
A11	UTV009	100	41.45	Nil	Nil	Nil

*cfu/ml= Colony forming unit per milliliter

Table 3. Results obtained from the Chemical and Microbiological analysis of various samples of Metronidazole suspension

Sample code	Batch No	Claimed strength (mg per 5ml)	Chemical analysis	Microbiological analysis		
			% content of Metronidazole	Bacteria count (cfu/ml)*	Fungi count (cfu/ml)*	Pathogen (cfu/ml)*
M1	UGS1012	200	105.27	Nil	Nil	Nil
M2	IC950006	200	100.00	Nil	Nil	Nil
M3	LOTMA448	200	109.72	Nil	Nil	Nil
M4	TMB49	200	69.44	Nil	10	Nil
M5	SPG018	200	104.10	Nil	Nil	Nil
M6	S4410	200	94.44	Nil	Nil	Nil
M7	LA86007	200	110.05	Nil	Nil	Nil
M8	11046	200	91.04	Nil	Nil	Nil
M9	LI006P	200	102.60	Nil	10	Nil
M10	BPL0317	200	109.91	50	10	Nil

*cfu/ml= colony forming unit per milliliter

DISCUSSION

All the samples used for this study were still within their shelf lives when analysis was carried out.The result on the analysis of the various samples of Paracetamol syrup revealed that all samples tested passed in terms of Bacteria, fungi and pathogen counts. It should be mentioned that common official specification allows for bacterial load of not more than 10^3cfu/g or ml, fungal load of not more than 10^2 and absence of pathogens in all oral pharmaceutical preparations (EP, 2007 and FIP, 1975). Three samples (P5, P7 and P10) with the highest number of bacteria count had only 10 cfu/ml which is far lower than the limit officially prescribed. The same

observation was made for the fungal count in samples P7 and P10. No product had any form of pathogens. The excellent result obtained from the microbiological analysis may be as a result of Good Manufacturing Practice in the various factories where they were produced. Good Manufacturing Practice excludes or minimizes microbial growths in all processes of production from raw materials procurement to finished product stages. In addition, the effect of the preservatives added to the formulations may also help to control the growth of microorganisms within the formulation. The Chemical analysis of the Paracetamol syrup samples however, showed that only five (5) samples passed in respect to the percentage content as regards official standard stated in the BP, 1998 which states that the content must range between 95% and 105%. Sometimes, it is a common practice for some factories to set in-house limits for content of active ingredient in their products, the values obtained for the six brands which failed based on the official standard are far too low and may result in incomplete action of the drugs when administered to children. Possible reasons for the low percentage content may include intentional or unintentional errors like error due to weighing machine, error due to calculation, intentionally weighing smaller quantities than required to cut cost, pilferage and use of substandard raw materials among other reasons. Others may include faking and counterfeiting of the drugs. These brands may therefore, be regarded as sub-standard, counterfeit or fake drugs. Thus, the chemical and microbiological analysis of these drugs showed that less than half of them are of the right quality and standard.

Looking at the analysis of the various samples of Ascorbic acid syrup used for this study, only one of the sample passed chemically (sample A10). Nine other samples gave percentage content of Ascorbic acid far lower than claimed by the manufacturer and far lower than official standard between 95% and 105% (BP, 1998). The possible reason for this low value may be attributed to formulation problem. Ascorbic acid has been found to readily undergo oxidation in liquid preparations and suitable methods are required to ensure that the active ingredient stay within permissible range throughout their shelf lives. Sample A8 however, showed percentage content of 113.19% also much higher than that claimed by the manufacturer and BP, 1998 specification. This may occur as a result of error, for example, error in weighing. It can be summarized that based on the result of the chemical analysis obtained, ten out of the eleven brands are counterfeit, fake or substandard. The microbiological analysis however revealed that ten out of the eleven the brands of Vitamin C syrup were within official limit and specification (EP, 2007 and FIP, 1975).

Brand A2 in addition to failing chemically, also showed pathogenic growth which according to official standard must be absent from oral liquid preparations. Presence of pathogenic organisms may portray contamination from sources like water, personnel or environment. Only brand A4 showed fungal growth of 10cfu/ml though all within acceptable limits. As earlier mentioned, the microbiological result obtained may also be attributed to Good Manufacturing Practice and effect of the preservative added to the formulation.

Microbial analysis of all samples of Metronidazole suspension showed that all samples passed according to specified standard. Pathogenic organisms were absent in all, three of the samples (M4, M9 and M10) had the highest fungal growth of only 10cfu/ml while only one of the sample (M10) recorded the highest bacterial growth of 50cfu/ml. Again, this shows possible Good Manufacturing Practice among manufacturers of these drugs and the effect of preservative added to the formulation. In addition, Metronidazole itself is an antibiotic which to a large extent may also inhibit the proliferation of microorganisms within the formulation. The chemical analysis on the other hand showed three of the brands (M4, M6 and M8) had percentage content of Metronidazole much lower than label claim and official standard (BP, 1998). Insufficient quantities of the antibiotic such as metronidazole in its dosage form have the ability of causing resistance by organisms susceptible to metronidazole in patients using them. Therefore, those brands with less than the required strength in the product may cause more harm to the child than good. Brand M7 was marginally higher than the official standard of 110% in BP, 1998.

CONCLUSION

The microbiological analysis of all the three types of oral liquid preparations gave satisfactory results. Only one brand of Ascorbic acid syrup failed the microbiological analysis.The Chemical analysis of the products however, can generally be said to be unsatisfactory. Six out of the eleven brands of Paracetamol syrup; ten out of the eleven brands of Ascorbic acid syrup and three out of the ten brands of Metronidazole suspension all failed the chemical analysis. Most of them recorded low percentage content of their active components in the various formulations. Manufacturers of these products should look into the method of formulation of these drugs to avoid sales of substandard drugs and promote manufacturing of drugs that are stable, safe and efficacious throughout their shelf lives. Also in conjunction with the regulatory bodies, manufacturers should device means of eliminating possible faking and counterfeiting of their drugs in the market.

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REFERENCE

1. Akunyili D. (2004). What are Fake counterfeit drugs? Pharmnews 26, p.43.
2. Ana-Maria Hossu; V. Magearu. (2004). Determination of Vitamin C in Pharmaceutical products with physic-chemical and bioanalytical technics. Vol. 9, no. 1: 1497-1504.
3. Ascorbic acid. At http://en.wikipedia.org/wiki/ascorbic_acid. Assessed on 01/06/2012.
4. British Pharmacoepia (1998) Vol. II: HM Stationery Office, London: 1492,1814
5. British Pharmacoepia (2007) Vol. III: HM Stationery Office, London: 2814- 2815
6. Carr AB, Einstein R, Lai LY, et al. (1981). Vitamin C and the common cold: using identical twins as controls. Med J Aust 2:411-2.
7. Cohen, S. H.; Gerding, D. N.; Johnson, S.; Kelly, C. P.; Loo, V. G.; McDonald, L. C.; Pepin, J.; Wilcox, M. H. et al. (2010). "Clinical Practice Guidelines for Clostridium difficile Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA)". *Infection Control and Hospital Epidemiology* 31 (5): 431–455.
8. Connors K. A.; Amidon G. L.; Stella V. J. (1986). Chemical Stability of Pharmaceuticals. New York: John Wiley.
9. Ecanow, B. (1984). Liquid medication. In dispensing of medication, 9th Ed.; King, R. E., Ed.; Mack Publishing Co.: Easton, PA,: 100- 139
10. FIP Working Party (2nd report, 1975). Microbiological purity of non-compulsory sterile pharmaceutical preparations. *Pharm. Acta. Helv*. 51: 33-40.
11. Heubi J. E.; Barbacci M. B.; Zimmerman H. J. (1998). Therapeutic misadventures with acetaminophen: hepatotoxicity after multiple doses in children. J. Pediatr 132: 22-27.
12. Ibezim, E. C.; Esimone, C. O.; Ofoefule, S. I., Chah, K. F. (2002). Evaluation of the Microbiological quality of some commercially available syrup and suspensions in Nig. J. Phytomed. Therap. 7 (1 &2): 18-25.
13. Kucers A, Crowe S, Grayson ML et al, eds. (1997). The use of antibiotics. A clinical review of antibacterial, antifungal, and antiviral drugs. 5th ed. Jordan Hill, Oxford: Butterworth-Heinemann: 936-58.
14. Lachapelle, M. Y.; Drouin, G. (2010). "Inactivation dates of the human and guinea pig vitamin C genes". *Genetica***139** (2): 199–207.
15. Larson A. M.; Ploson J.; Fontana R. J. et al. (2005). Acetaminophen-induced acute liver failure: results of a United States multicenter. Prospective study; Hepatology 42(6): 1364-72
16. Lesko, S. M.; Mitchell, A. A. (1999). The safety of acetaminophen and ibuprofen among children younger than two years old. Pediatrics 104 (4).
17. Metronidazole. At http://en.wikipedia.org/wiki/metronidazole. Assessed on 01/06/2012.
18. Microbiological Quality of Pharmaceutical preparations. European Pharmacopoeia 5.6 (2007): 4451
19. Paracetamol. At http://en.wikipedia.org/wiki/paracetamol. Assessed on 01/06/2012.
20. Rivera-Penera T.; Gugig R.; Davis J. et al (1997). Outcome of acetaminophen overdose in Pediatric patients and factors contributing to hepatotoxicity. J. Pediatr 130: 300-304.
21. Shami, E. G.; Bernardo, P. D.; Rattie, E. S.; Ravin L. J. (1972). Kinetics of Polymorphic transformation of sulfathiazole form I. J. Pharm. Sci. 61: 1318-1321.
22. Stone, Irwin (1972). The Natural History of Ascorbic Acid in the evolution of mammals and primates. At http://www.seanet.com/~alexs/ascorbate/197x/stone-i-orthomol_psych-1972-v1-n2-3-p82.htm. Assessed 16-04-2012.