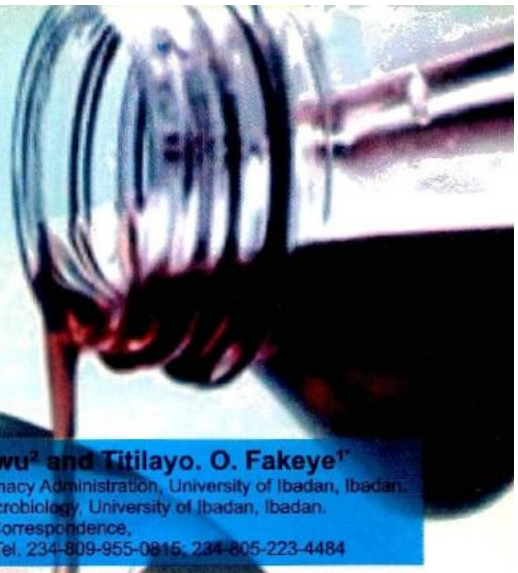
ORIGINAL RESEARCH

Potential Dangers of Administering Undiscarded Paracetamol Syrup



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ABSTRACT

Background: Paracetamol is one of the most commonly used over-the-counter (OTC) drugs as adjunct for children with feverish condition. Paracetamol syrup may be susceptible to microbial growth because of presence of sugar. Considering the health hazard to children, it is imperative to evaluate the type of microbial contaminations that may be present in bottles of paracetamol that have been opened for use.

Methods: Questionnaires were administered to 150 parents and caregivers of children below five years of age to evaluate their level of awareness of the proper storage conditions of paracetamol syrup and the potential dangers for re-using undiscarded syrup for their children/wards. Microbial assessments were carried out on 10 bottles of paracetamol syrup randomly collected from the caregivers/parents who brought children for immunization to evaluate the microbial load. Standard methods of microbial isolation were employed and the various isolates were subjected to morphological and biochemical tests for identification. Descriptive statistics was used to summarize data.

Result: There was a poor level of awareness on the proper storage of paracetamol syrup as well as a low level of awareness on the potential dangers of administering contaminated paracetamol syrup in the form of reuse of undiscarded syrup to children.
Pathogenic bacteria such as Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli and Klebsiella species and fungi, Rhizopus species, Mucor species, Aspergillus species, Candida species and Penicillium species in different loads were isolated from the samples of undiscarded paracetamol syrup.

Conclusion: The re-use of paracetamol syrup not properly stored is potentially hazardous for children. There is a need for creating awareness on the proper storage of paracetamol syrup that has been opened for use, and the likelihood of microbial contamination of such syrups.

Key words: Paracetamol syrup, pediatric patients, contamination, microbial assessment.

INTRODUCTION

Oral liquid formulations are popular non-sterile dosage forms of administering active medicaments to babies, children and the elderly[1]. Concentrated aqueous solution of sucrose or other sugars serve as the general vehicle for some of these oral liquid formulations, making the taste acceptable to the patient among other reasons. Contaminating yeasts and molds can however develop readily in medications made with syrup[1]. Microbial contamination, which could be due to pathogenic microorganism, may also cause spoilage or degradation, which could lead to spoilage of medicaments[2]. Contaminated preparations deteriorate rapidly, leading to reduction in their shelf-life and efficacy[3, 4, 5]. Hugo and Russell (1980) reported microbial degradation of drugs like alkaloids, barbiturates, analgesics and steroids resulting in marked reduction or complete abolishment of therapeutic efficacy[5]. Microbial contamination of oral pharmaceuticals may also change the physical, chemical, and organoleptic properties of the drugs, alter the contents of active ingredients, or convert them to toxic products[7,8,9].
The International Pharmaceutical Federation's Working Party has provided the standard numerical tolerance of microbes in liquid oral preparations as 10^3 bacteria cells/g or mL and 10^2 fungi or yeasts cell/g or mL; while the presence of pathogenic organisms such as *Pseudomonas aeruginosa*, *Salmonella species*, *Staphylococcus aureus*, *Escherichia coli* and the Enterobacteriaceae are totally excluded[3]. Physicochemical deterioration as a consequence of microbial growth is a satisfactory reason to consider the product unsafe for human use[9]. The presence of even a low level of acutely pathogenic microorganisms, higher levels of opportunist pathogens, or toxic microbial metabolites that persist even after death of the original contaminants may render the product ineffective. Some of these toxin-related illnesses include acute gastroenteritis, abdominal discomfort, and diarrhea. Symptoms vary from mild gastric distress to death, depending on individual susceptibility to the toxin, amount of ingested toxin, and general health of the victim[10, 11].
Microbial contamination of non-sterile products was one of the

major reasons for product recalls and production shutdowns at the beginning of the 21st century[12]. Though the quality of raw materials used in manufacturing will ultimately determine the value of the finished product, most drugs get contaminated after production either through storage or during dispensing[13,14,15].

Paracetamol is the most common over the counter (OTC) drug used for self-medication by mothers in the age group 12 years and below[16,17,18]. It is also the most widely used analgesic and antipyretic due to its safety profile[19].

There exist the possibilities of contamination with re-use of syrups several weeks after opening a new bottle of liquid medication for oral use. Considering the frequency of use of paracetamol syrup, the over-the-counter status, and the fact that parents and caregivers may indulge in the practice of keeping the remainder of paracetamol syrup for re-use whenever the need arises, this study was carried out to evaluate microbial status of paracetamol syrup when the contents are not fully used the first time. The study also evaluated the level of microbial contamination of the content of the bottles of paracetamol syrup remaining after administration of one or more doses.

METHODS

Study Population and Site

Patients and caregivers of children below the age of 5 years attending St. Mary's Catholic Hospital, a secondary health care facility in Ibadan, were recruited into the study between 31st January and 4th March, 2011.

Included in the study were caregivers who brought children to the hospital for immunization and who gave their consent to participate in the study after the aims and objectives of the study had been explained to them.

Study Design

A cross-sectional survey was conducted between 31st January and 4th March, 2011 after written approval was obtained for the study at the St. Mary's Catholic Hospital, Ibadan. The essence of the study was explained to the mothers/caregivers of the children on each immunization date between 31st January and 4th March, 2011. A questionnaire evaluating among other things socio-demographic characteristics of the respondents; the level of understanding of the reasons for use, storage conditions, possibility of contamination, and for how long they would keep administering paracetamol syrup after first use before such would be discarded was pretested using five mothers to assess the design of the questionnaire for ambiguity and ease of understanding. The mothers used for pretest were excluded from the study. One hundred and fifty questionnaires were finally administered to mothers and caregivers using systematic randomization method. Mothers/caregivers of every second child of the age 1 to 5 years whose immunization card was dropped at the nurses' table for immunization was approached for recruitment. When the mothers/caregivers were willing to participate, they were assisted in filling the questionnaire. This was done until the 4th March, 2011.

The second part of the study evaluated the microbial load of paracetamol syrup collected from caregivers/parents. Ten opened bottles of paracetamol syrup were collected from caregivers/parents who brought the bottles along with them to the hospital during the period of the study. New bottles of paracetamol syrup were given to compensate for the one collected. The collected samples were kept in a refrigerator. Information on when the bottles were first opened was obtained from the caregivers. Standard methods of microbial isolation were employed and the various isolates were subjected to morphological and biochemical tests[20].

Microbial analysis was done by taking 1ml aliquots from each of the syrups aseptically, using appropriate serial dilution to estimate viable microbial count. Colonies were estimated with the aid of a colony counter and expressed as colony forming unit (cfu) after incubation at 37°C for 24 hours (for bacteria), and at 25°C for 7 days for fungi. Gram-staining was done on the bacteria colonies to distinguish the Gram-positive organisms from Gram-negative organisms. Selective media were used to isolate specific bacteria and fungi genera: Mannitol salt agar (Lab M) for *Staphylococcus aureus*, MacConkey agar (Lab M) for coliforms, Cetrimide agar (Lab M) for Pseudomonas spp and Sabouraud dextrose agar (Lab M) for fungi. Morphological characteristics were further used to identify specific organisms. Biochemical tests such as citrate, indole and urease tests were carried out to identify specific organisms using the standard methods of Cheesbrough[20].

Data Analysis

The generated data were analyzed using SPSS window version 17.0 software. Descriptive statistics were used to summarize the data while Chi square test was used to investigate association between respondent's socio-demographic characteristics and their responses.

RESULTS

One hundred and seven respondents (71.3%) were female and 43 (28.7%) were male. One hundred and thirty-eight (92.0%) were married, 10 (6.7%) single and two (1.3%) divorced. Twenty-eight respondents (18.7%) were 20-29 years; 87 (58.0%) were 30-39 years; 32 (21.3%) were 40-49 years; three (2.0%) were 50-60 years. Eight respondents (5.3%) had primary education, 25 (16.7%) had secondary while 113 respondents (75.3%) had tertiary education and 2 respondents (1.3%) had no formal education. Relationship to patients showed that 99 (66.0%) were mothers; 41 (27.3%) fathers; two (1.3%) grandmothers; one (0.7%) aunt; two (1.3%) family friends, and three (2.0%) were brothers.

One hundred and thirty-three respondents (88.7%) would keep

the remaining syrup after dosage completion, 14 (9.3%) would discard and three (2.0%) did not respond. Forty-five respondents (30%) would keep the remainder of the syrup in a refrigerator while others will keep it outside a refrigerator. Sixty-three respondents (42.0%) would keep bottles of paracetamol syrup for over one month after the first use; 25 (16.7%) would use for four weeks after opening the syrup and discard while 62 (41.3%) would discard between one and three weeks after use.

The various reasons for keeping the remaining paracetamol syrup revealed the following: to reuse (82; 68.3%); to save cost (29; 24.2%); yet to finish (2; 1.7%); prevent wastage (4; 93.3%); there was no instructions not to re-use (1; 0.8%) and well preserved in refrigerators (2; 1.7%). Thirty-six (28.1%) were informed about how long to keep the used paracetamol syrup before disposal while 92 (71.9%) were ignorant. Ninety-five (63.3%) respondents were not informed of the specific period to keep used paracetamol syrups for re-use. Fifty-eight (38.7%) respondents were not aware of the possibilities of the syrup being contaminated after prolonged use. Eighty-seven (38.7%) were not aware that there is a safe period which is two weeks.

Microbial analysis of the samples of paracetamol syrup collected from the mothers showed presence of some pathogenic bacteria such as *Escherichia coli*, and fungi such as Aspergillus species (Table 1). The urease test was negative for the enterobacteriaceae isolates while the indole test was positive for 13 (76.5%) isolates and citrate test was positive for 4 (23.5%) isolates. The biochemical tests to ascertain the identity of the enterobacteriaceae revealed that colonies A1, A2, A5, A6, C1, C2, C4, C5, G1, G2, G4, H1 and J1 were Escherichia coli while A3, A4, C3 and G3 were Klebsiella pneumonia (Table 2).

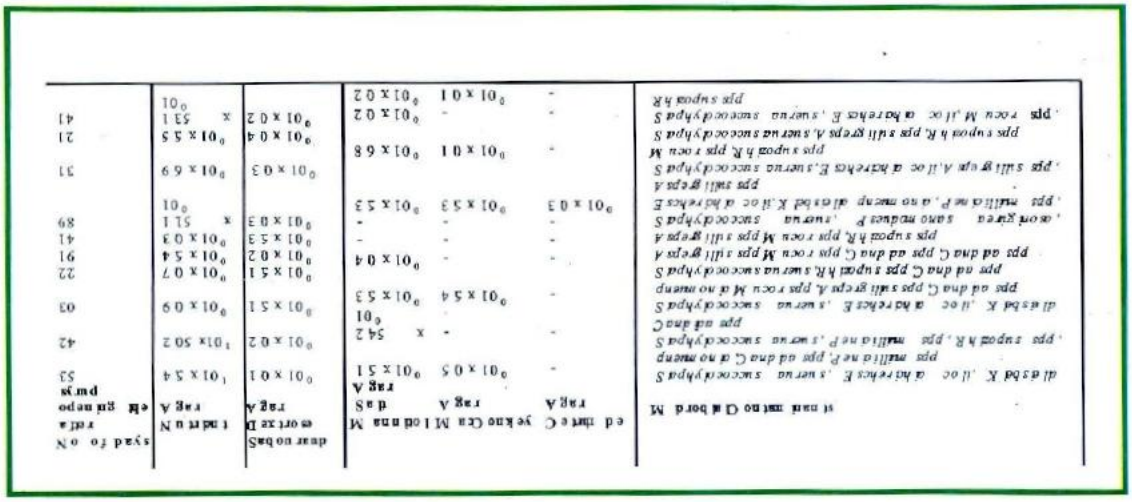

Table 2: Biochemical Test Results to identify the Enterobacteriaceae Isolates Present in Samples

Isolates	Citrate	Indole	Urease	Enterobacteriaceae Isolate
A1	-	+	-	*Eschericia coli*
A2	-	+	-	*Eschericia coli*
A3	+	-	-	*Klebsiella pneumonia*
A4	+	-	-	*Klebsiella pneumonia*
A5	-	+	-	*Eschericia coli*
A6	-	+	-	*Eschericia coli*
C1	-	+	-	*Eschericia coli*
C2	-	+	-	*Eschericia coli*
C3	+	-	-	*Klebsiella Pneumonia*
C4	-	+	-	*Eschericia coli*
C5	-	+	-	*Eschericia coli*
G1	-	+	-	*Eschericia coli*
G2	-	+	-	*Eschericia coli*
G3	+	-	-	*Klebsiella pneumonia*
G4	-	+	-	*Eschericia coli*
H1	-	+	-	*Eschericia coli*
J1	-	+	-	*Eschericia coli*

Key:
- : negative
+ :positive
A-J: Samples of paracetamol syrup
1-6: Isolated colonies from the paracetamol syrup

DISCUSSION

This study revealed a relatively low level of awareness of the possibilities paracetamol syrup being contaminated with reuse. About one third of the sample population was not aware of the likelihood of contaminations and would administer the remaining paracetamol syrup in the opened bottle for over a month. Less than one third of the respondents would refrigerate the syrup while the rest would not. Refrigeration, which is a means of limiting the growth of microorganisms, could not be relied on due to the unstable nature of power supply in Nigeria. This makes refrigeration a questionable means of proper preservation against microbial spoilage in Nigeria. The extent of contamination differed from one user to the other.

There was evidence of inadequate counseling by pharmacists since only one fifth of the respondents were told to discard the syrup after use. This however could be due to oversight, assuming the patient knows, or no plan to counsel on the part of the pharmacist. It is therefore needful to communicate the findings of this research to Pharmacists with a view to rekindling the desire to engage in detailed patient counseling.

Expectedly, the sample that had been opened for the highest number of days had the heaviest microbial load and the one opened for the least number of days had the least microbial load (Table 1). This showed there might be a relationship between the days post opening of the syrup and the microbial load for most of the samples. However, storage condition, maintenance of good hygiene among other factors could also have played a role in the microbial load.

The International Pharmaceutical Federation's Working Party has provided the standard numerical tolerance of microbes in liquid oral preparations as 10^3 bacteria cells/g or ml and 10^2 fungi or yeasts cell/g or mL; the presence of *Pseudomonas aeruginosa*, Salmonella species, *Staphylococcus aureus*, *Escherichia coli* and the *Enterobacteriaceae* were totally excluded[3]. Although none of the paracetamol syrups exceeded the standard numerical tolerance limits of microbes, the presence of pathogenic microorganisms such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli* and *Klebsiella species* as is seen in some of the samples is not permitted and implies that the syrups could be hazardous when administered[21,22].

The microorganisms isolated from

these syrups are implicated in various infections. Staphylococcus aureus, though not always pathogenic, may cause a range of illnesses from minor skin infections, such as pimples, impetigo, boils (furuncles), scalded skin syndrome and abscesses, to life-threatening diseases such as pneumonia and sepsis. It is also implicated in nosocomial infections, often causing postsurgical wound infections[13]. Some species of *Aspergillus* are pathogenic in humans and animals by producing aflatoxin which can potentially contaminate foods[13]. *Rhizopus species* is implicated in mucormycosis and causes certain pulmonary and cutaneous infections. Penicillium species cause pulmonary fibrosis, pulmonary infections, endocarditis, peritonitis, endophthalmitis and oesophagitis[13]. Virulent strains of *Escherichia coli* may cause gastroenteritis, urinary tract infections and neonatal meningitis. In rare cases, it is responsible for hemolytic-uremic syndrome, peritonitis, mastitis, septicemia, and Gram negative pneumonia[22]. *Candida species* is responsible for candidiasis. *Klebsiella pneumonia* causes destructive changes to human lungs, inflammation and hemorrhage with necrosis. It may also cause urinary tract infection, lower biliary tract infection and surgical wound sites. An opportunistic, nosocomial pathogen of immune-compromised individuals, *Pseudomonas aeruginosa* typically infects the pulmonary tract, urinary tract, burns, wounds and also causes blood infections[18].

There is obviously a need to educate mothers and caregivers about the potential dangers inherent in the re-use of paracetamol syrup. For example, the media could be used to inform the general populace of the likelihood of contamination and therefore the necessity to discard the remaining paracetamol syrup after dosage completion or after a specific period after the first use.

This study was limited by the fact that the results could not be said to be due to particular brand(s) of syrup used. Several brands were collected from the parents/caregivers

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CONCLUSION

Administration of used paracetamol syrups to children may pose a health threat on account of possible contamination of the syrup by microorganisms. Based on the findings of this study, it is obvious that there is a poor level of awareness of the possibilities of administering contaminated paracetamol syrup. It can also be said that keeping used paracetamol syrups for re-use at a later date encourages contamination by pathogens. It is therefore imperative that healthcare givers, especially pharmacists create awareness on the possible contamination of paracetamol syrup if not disposed of at the proper time and the danger it poses, and counsel patients appropriately.

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