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A REVIEW:- INSTABILITY IN PAEDIATRIC DRY SYRUP OF ANTIBIOTICS

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ABSTRACT

Oral paediatric suspensions of antibiotics are mainly available as dry powders for reconstitution. Most of reconstituted antibiotic suspension is to be kept refrigerated in order to get the optimal therapeutic action from the drug. However many patients do not keep to it to specified storage conditions for many reasons. Like no refrigeration and irregular power supply that may result in various degree of degradation of reconstituted antibiotics. Pharmacists are therefore challenged how to counsel patients when there is no refrigeration or erratic power supply.[1] Inappropriate use of antibiotics leads to economically and clinically preventable negative consequences including unnecessary adverse effects, increase mortality and morbidity from treatment failure, wasting healthcare resources, and increase the emergency of bacterial resistance.[2] Improper storage condition leads to physical instability, chemical instability, reduction in potency, or it may also leads to serious adverse effect on the patient's health. Therefore storage conditions for reconstituted liquids must not be taken lightly. Present review will discuss instability problems associated with dry syrup of antibiotic and its feasible remedial measure, like proper storage condition, use of stabilizer, different packaging material.

KEY WORDS: Antibiotic, stability, paediatric dry syrup, resistance.

1. INTRODUCTION

1.1 Paediatric dry syrup

Dry syrup are dry mixtures containing the drug and suitable suspending and dispersing agents to be diluted and agitated with a specific quantity of vehicle, most often purified water.

Stability is defined as the capability of a drug substance or drug product to remain within the established specifications, to maintain its identity, strength, quality, and purity throughout the retest or until expiry date period.[1]

The reconstituted system is the formulation of choice when the drug stability is major concern. The medications are supplied in dry form because the product can be stored for a long time in dry form but becomes unstable and deteriorates in solution within a relatively short time. Such solutions are said to have a "short shelf life". For example, reconstituted suspension of penicillin has a maximum shelf life of 14 days. The manufactured dry mixture, however, has a shelf life of at least 2 years.[3] Augmentin dry powder has a shelf life of 24 months when stored below 25°C. and its reconstituted powder have a shelf life of 7 days when stored at 2°C to 8°C.[4]

Another reason of prescribing antibiotics as dry syrup for infants and young children are children's inability to swallow tablets or capsules; unavailability of certain antibiotics in a chewable tablet form; and the discomfort, expense and associated risk of antibiotic injection.[2]

The process of reconstituting medications from powder to liquid form would be expected to cause more errors than dosing with ready-to-use liquid drugs. Errors could occur with regard to the reconstitution process, the volume and temperature of the reconstituted liquid, the medication shelf life, storage conditions and accurate dosing.[5]

Stability studies have demonstrated that the dry oral suspension after constitution in a liquid is stable for 24h after preparation; reconstituted solution remains stable when stored in the refrigerator for the labeled period, usually 7 to 14 days, depending on the preparation. This is sufficient period for the patient to complete the regimen usually prescribed. However, in case the medication remains after the patient complete the course of therapy, the patient should be instructed to discard the remaining portion, which would be unfit for use at the later time.[3]

Liquid formulations generally tend to have much shorter shelf-lives than solid formulations and once opened it should be used within 2 weeks to avoid any microbial contamination or reduction in activity. The nature of dry syrup formulations in terms of added adjuncts such as sweetening, flavouring, suspending, stabilizing, and preserving agents make the liquid formulation a complex one that is very prone to physical, chemical and microbiological instability.

1.2 Why we require special attention to this antibiotic instability issue

In countries like India Doctor will give you antibiotics prophylactically, as a way to prevent infection. This should only be done in very extreme cases because it's spreading resistance. Antimicrobial resistance in pathogens causing important communicable diseases has become a matter of great public health concern globally including our country. Resistance has emerged even to newer potent antimicrobial agent like carbapenems.

It is found that about half of the antibiotics prescribed to the children are unnecessary.[6]

Article: Major Delhi study identifies germs behind untreatable sepsis, pneumonia

The study has found that babies infected with 'superbugs' in birth facilities within 72 hours of being born, thousands of Indian babies are dying due to an 'alarming degree' of drug resistance. The researcher found that nearly 26% of babies with sepsis died, as multi drug resistance made the ailment untreatable. Estimates also indicate that 56,524 babies die each year from resistance to first line antibiotics. Study result highlighted the big threat to efforts aimed at containing infant mortality rates.

Antibiotic resistance is a global public health threat, but nowhere is it as stark as in India. The crude infectious disease mortality rate in India today is 416.75 per 100,000 persons, twice the rate in the U.S. (200) when antibiotics were introduced.[7]

In India almost 100% of the healthy population carries bacteria that are resistance to ampicillin, ciprofloxacin, trimethoprim, nalidixic acid and chloramphenicol.[6]

1.3 Impact on drug resistance

Antibiotics are misused because many patients do not take them according to their doctor or pharmacist instructions. They may stop tacking their antibiotics too soon, before their illness is completely cured.[2]

In many countries it is possible to buy antibiotics over the counter. Often, if people are poor they will not take the full dose-all of that leads to resistance.

Inappropriate use of antibiotics leads to economically and clinically preventable negative consequences including unnecessary adverse effects, increase mortality and morbidity from treatment failure, wasting healthcare resources, and increase the emergency of bacterial resistance.[2] The rapid emergence of resistance bacteria is occurring worldwide, endangering the efficacy of antibiotics. It is also making some disease, such as meningitis or pneumonia, more difficult to treat. We might need stronger, more expensive drugs, we might need to take them longer. We also might not get well as quickly.

All major resistance control strategies recommend education for patients, children, the public and relevant health care professional regarding unique features of bacterial infections and antibiotics, prudent antibiotics prescribing as a positive construct, and personal hygiene.

The center for Disease Control and Prevention (CDC), as well as other organization and experts, recommends various steps that health care practitioners (HCPs) and facilities can pursue to reduce antibiotic resistance, such as adopting an antibiotic stewardship program; improving diagnosis, tracking and prescribing practices; optimizing therapeutic regimens; and preventing infection transmission. Antibiotic stewardship involves making a commitment to use antibiotics only when needed, choose the proper drug, and administer the medication at the appropriate dose and duration in every case.[8]

Drug utilization evaluation studies are required for antibiotics in children because use of antibiotics in hospitals account for 20-50% of drug expenditures. It is found that about half of the antibiotics prescribed to the children are unnecessary.[6]

1.4 How we can solve antibiotic resistance and dry syrup instability issue?

In 2012 Indian Council of Medical Research (ICMR) started a program on antibiotic stewardship to tackle resistance issue. Indian academy of Paediatrics (IAP) joined hands with ICMR in 2014 to discuss and deliberate over the magnitude of the problem, reasons and possible solution to tackle the antimicrobial resistance among children in India.[9]

Table 1: List of commonly available antibiotic dry syrup paediatric formulation in Indian market.[3]

Sr. No.	Antibiotic	Brand Name
01.	Amoxycilin	AmoxicoR Amoxil Forte Amoxil
02.	Amoxycilin with potassium clavulanate	Augmentin DS Amonil-CV dry syrup Clavam dry syrup Trimoclav dry syrup Lexiline- CV dry syrup Avox 228.5 dry syrup Estamox-CV 457 suspension
03.	Cefuroxime	Ceftin Oral suspension Zinnat Suspension
04.	Cefuroxime with potassium clavulanate	Zefu-CV dry syrup Zocef CV dry syrup Covatil CV dry syrup
05.	Cefixime	Taxim-O dry syrup Cefixid-DS dry syrup Linicef dry syrup Sectocef 100 dry syrup
06.	Cefixime with potassium clavulanate	Rovixim-Clav Cefex-CV Cefiza-CV Cefidol-CV Rezix-CV
07.	Cefpodoxime	Nupod DS Estidox dry syrup Alucef forte
08.	Cefpodoxime with potassium clavulanate	Bioxim-CV Ruhopod-CV Wildox-CL dry syup Pod fed-CV
09.	Cefixime and ofloxacin	Necfix-O
10.	Cephalexin	Phexin DS Enceff dry syrup Alucef Forte
11.	Cefadroxil	Kefloxin DS
12.	Azithromycin	Azimax 200 dry syrup Azithron dry syrup

Table 2: Paediatric antibiotic oral suspensions – storage recommendations.[10]

Generic name	Trade name	If at room temperature, can be kept up to…..	If refrigerated, can be kept up to…….
Amoxicillin	Amoxil	14 days	14 days (refrigeration preferred but not required; improves taste)
Amoxicillin/ Clavulanate	Augmentin DS Trimoclav DS	Do NOT leave at room temperature. (only kept out when giving the dose)	10 days
Azithromycin	Azimax 200 DS	10 days	10 days
Cefuroxime	Zinnat Suspension	3 days	10 days
Cephalexin	Phexin DS	1 day	14 days
Cefprozil	Nupod DS	1 day	14 days

2. REPORTED STABILITY ISSUE FOR PAEDIATRIC DRY SYRUP OF ANTIBIOTICS

An appropriate storage condition for reconstituted antibiotic is defined as keeping the medicines under refrigeration (2-8°C).

Many homes in rural areas of developing nation may not have refrigerators or lack power supply, and even where there is refrigerator and power supply there may be erratic supply. Therefore medicines are stored at room temperature or kept in fridges that have no power supply for several hours in a day thereby exposing these drugs to excessive temperatures far more than the room temperature which ultimately may cause decomposition of both the excipients and active ingredient(s).[1]

Penicillin and cephalosporin are usually prescribed with clavulanic acid as potassium salt. Clavulanic acid is beta-lactamase inhibitor. The stability of potassium clavulanate is very low in their formulation of dry powder for reconstitution. John N.A. Addotey carried out studies on stability of reconstituted powder of co-amoxiclav and stated that standard storage condition for co-amoxiclav is 2°C - 8°C. Even if proper storage condition is not provided some brands of co-amoxiclav shows browning coloration from 4th day and partitioning into two distinct phases and it gets increased day by days. This shows physical instability.

Reported stability methods

Mehta et al. carried out studies on Augmentin by using HPLC to determine the chemical stability of amoxycillin and potassium clavulanate in 250/62 oral suspension. It was stored at room temperature (20°C) and 8°C over a period of 11 days.

During the test period, the amoxycillin component was found to be more stable than the clavulanate. Amoxycillin was stable for 7 days at both temperatures. Potassium clavulanate maintained at least 90% of its initial concentration for 7 days at 8°C but showed more than 40% degradation in the same time period at room temperature. For potassium clavulanate the shelf-life or time taken for the original concentration to drop to 90% of its value at room temperature was found to be 2 days.[11]

Adulkarim Kassem Yehia Al Zomor et al. carried out study on Cefuroxime axetil 125mg/5ml (Zinnat) oral suspension at room temperature (25°C) and stored in refrigerator (2-8°C).

Reconstituted Cefuroxime axetil stored at refrigerator (2-8°C) is stable for 10 days over 90%, after that start to degradation. While concentration percentage of Cefuroxime axetil stored at room temperature were over 90% up to 5^{th} day, degradation was extensive by 7^{th} day with cefuroxime axetil concentration failing to 80% outside the acceptance limits. Cefuroxime axetil suspension after reconstitution was found stable for 10 days, if stored at refrigerated condition but 3 days only at room temperature.[12]

Dan Diaconu et al. carried out study on stability of powder for oral suspension containing 250mg Cefadroxil and 100mg Cefixime/5ml.

Cefadroxil in suspension is stable during 9 days in the refrigerator and 7 days at room temperature. Cefixime in suspension is stable during 8 days in refrigerator and 6 days at room temperature. The study shows that the suspension can be administered during 6 days if kept at 25°C, and 8 days if kept in refrigerator.[13]

3. REMEDIAL MEASURES

3.1 Patient education program

Patient should be properly educated to fight against instability of dry syrup of antibiotic and subsequent issue of antibiotic resistance.

Patient counseling must be done for following issue:
Don’t take antibiotics unless it is need.
An estimated 30% of millions of prescription written each year not needed.

Always ask your doctor if antibiotic will really help. For illness caused by viruses- common cold, bronchitis, and many ear and sinus infections don’t require antibiotics.

Finish your dosage regimen. Take your entire prescription as directed exactly. Do it even if you start feeling good. If patient should stop taking antibiotics bacteria's are more likely to become drug resistant.

An appropriate storage condition for reconstituted antibiotic is keeping the medicines under refrigeration (2-8°C).

Get vaccinated. Immunizations can protect you against some disease that is treated with antibiotics. E.g. Tetanus, whooping cough.

Maintain proper hygienic conditions specially in hospitals.[6]

3.2 Use of different packaging material

Patent: Pharmaceutical formulation comprising Amoxycilin and clavulanate

EP 1078627 A1

In the formulation of this invention, amoxycillin may be in form of sodium amoxycillin, or, amoxycillin trihydrate. Clavulanate is preferably in the form of potassium clavulanate. Potassium clavulanate is extremely moisture-sensitive and should be stored and handled in conditions of 30% RH or less, ideally as low as possible.

So formulation of the present invention are preferably provided in an atmospheric moisture-proof container or a sachet for reconstitution with water or other suitable aqueous medium shortly prior to use. Preferably, a dry powder formulation is provided in a bottle with a moisture-proof cap.[14]

3.3 Paediatrician workshop

In 2012, ICMR started a program on antibiotic stewardship program to prevent emergence of antibiotic resistance. Under this workshop is running to train the participants. Indian academy of Paediatrics joined hands with ICMR in 2014 to discuss and deliberate over the magnitude of the problem, reasons and possible solution to tackle the antimicrobial resistance among children in India.[9]

3.4 IAP-ICMR plan to tackle antimicrobial resistance

1. Developing and disseminating National Antibiotic Guidelines for Children 2014 – The IAP-ICMR document

2. Educating doctors – both paediatricians and other doctors – as well as public on rational antibiotic use.
3. Developing infection control guidelines for small hospitals and nursing homes, training the owners of such establishments and ensuring compliance by the members.
4. Collecting and collating data on antimicrobial resistance from the clinicians.[9]

3.5 Legal restrictions

To make agencies like the Centers for Disease Control and Prevention to create a tougher surveillance system to monitor the use of antibiotics in hospitals and other medical settings. It includes specific steps that hospitals participating in Medicaid and Medicare must take to reduce inappropriate use of antibiotics.[15]

With the recognition of the various challenges noted with antibiotic use in paediatric and neonatal population, Paediatric Infectious Disease Society (PIDS) in 2010 formed the Paediatric Committee of Antimicrobial Stewardship with the mission of advancing paediatric antimicrobial stewardship in various clinical settings, promoting research, and developing antimicrobial stewardship educational programs.[9]

3.6 Use of stabilizer in formulation

Patent: Pharmaceutical formulation for sulfur containing drugs in liquid dosage forms WO 2007067331 A1

Stabilizer added as one of excipients can extend the stability of the pharmaceutical formulation liquid dosage form of d-penicillamine for a period of at least 30 days when the formulation is stored below room temperature.

When the sulfur containing active agent is metal chelator. E.g. d-penicillamine and it is formulated as dry syrup for reconstitution stability of the active agent in formulation is issue. This invention includes sulfur containing active agent d-penicillamine and disodium dehydrate ethylene demine tetra acetate (EDTA) as a stabilizer. Addition of an appropriate amount of EDTA may increase the stability of refrigerated liquid dosage formulations of d-penicillamine for a period in excess of 30 days.[16]

Patent: Pharmaceutical formulation comprising Amoxycilin and clavulanate EP 1078627 A1

The formulation of this invention will include, in addition to its active materials amoxicillin trihydrate and potassium clavulanate, excipients such as suspension aids, glidants, diluents, bulking agent, sweetening agent, stabilizers, pH modifiers, preservatives, etc. In addition formulation also comprise desiccant to assist preservation of potassium clavulanate against hydrolysis by atmospheric moisture on storage. Potassium clavulanate is normally supplied in admixture with silicon dioxide as diluents, typically as a 1:1 blend.[14]

3.7 Proper storage condition

The dry powder should be stored at room temperature. Antibiotic dry syrup after reconstitution it should be stored in refrigerator (2-8°C). Freezing should be avoided to prevent aggregation.

CONCLUSION

Antimicrobial resistance has emerged as a major public health problem all over the world. Reconstituted solution remains stable for 7 to 14 days when stored in refrigerator. But because of many reasons proper storage condition could not be available which leads to degradation of product. Medication remains after complete course of therapy, patient should be instructed to discard remaining portion. Patient counseling on proper storage condition and on its resistance issue is necessary when antibiotic is given in dry syrup formulation. To increase stability of reconstituted suspension various remedial measures could be taken like by adding stabilizers, by proper storage condition, by using different packaging. In 2012 Indian Council of Medical Research (ICMR) started a program on antibiotic stewardship to tackle resistance issue.[9]

ABBREVIATIONS

U.S. - United States

CDC - Center for Disease Control and Prevention

HCPs - Health care practitioners

ICMR - Indian Council of Medical Research

IAP - Indian academy of Paediatrics

HPLC - High performance liquid chromatography

PIDS - Paediatric Infectious Disease Society

EDTA - Ethylenediaminetetraacetic acid.

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